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(54) Title: HUMAN ANTI-ADIPOCYTE MONOCLONAL ANTIBODIES AND THEIR USE

(57) Abstract: A panel or library of antibodies that bind adipocyte antigens, methods of obtaining isolated antibodies and antibody variable domains and mixtures thereof, uses in identifying antigen molecules, in assays, diagnostically and therapeutically.

HUMAN ANTI-ADIPOCYTE MONOCLONAL ANTIBODIES AND THEIR USE

The present invention relates to antibodies directed to adipocytes and particular antigens on adipocyte surfaces. It further relates to libraries and panels of antibodies which may be screened for identification of antibodies useful in particular contexts, which may be used in a variety of contexts, including identifying adipocyte antigens.

10 Obesity is a disease characterised by a pathological increase in adipose cell mass. As a disease it is becoming more prevalent, with over 50% of adults in the UK already overweight and 1 in 5 of those now clinically obese. Consequently, over recent years there has been a marked 15 increase in adipocyte research, the cell type responsible for storage of excess lipid. For many years the adipocyte was believed to be a relatively dormant cell type, acquiring or losing lipid stores in response to regulatory signals from other cells. However, recent research has demonstrated that 20 adipose tissue is actively secreting metabolic regulators and that these play a key role in energy homeostasis and food intake.

25 The most well known adipocyte signalling molecule identified to date is leptin. Leptin, a 16KDa protein encoded by the ob gene, is secreted by adipocytes in concentrations directly proportional to body fat mass (Zhang et al., (1994) *Nature* 372: 425-432; Rosenbaum et al., (1996) *J. Clin. Endocrinol. Metab.* 81: 3424-3427). Although the biological role of leptin 30 has not been fully deduced, it has been shown in mice to bind a receptor in the hypothalamus and induce satiety (Tartaglia et al., (1995) *Cell* 83: 1263-1271; Chen et al., (1996) *Cell* 84: 491-495; Lee et al., (1996) *Nature* 379: 632-635). Systemic or intracerebroventricular administration of leptin 35 decreases food intake and results in reduced body fat

(Schwartz et al., (1996) *Diabetes* 45: 531-535; Halaas et al., (1995) *Science* 269: 543-546; Pelleymounter et al., (1995) *Science* 269: 540-543; Campfield et al., (1995) *Science* 269: 546-549). Moreover, in ob-ob mice, which are very obese, the 5 ob gene is mutated so that no leptin is produced; when administered leptin, the mice stop eating and rapidly lose weight (Pelleymounter et al., (1995) *Science* 269: 540-543; Halaas et al., (1995) *Science* 269: 543-546). One of the ways 10 in which leptin acts is by down-regulating expression of the appetite-stimulating peptide NPY (neuropeptide-Y) (Stephens et al., (1995) *Nature* 377: 530-532; Schwartz et al., (1996) *Diabetes* 45: 531-535). High concentrations of NPY promote 15 eating, and intracerebroventricular infusions of NPY can cause obesity in normal rats (Stanley et al., (1986) *Peptides* 7: 1189-119). In ob-ob mice, the beneficial effects of 20 administering leptin are accompanied by a marked decrease in hypothalamic NPY concentrations (Stephens et al., (1995) *Nature* 377: 530-532). However, transgenic mice lacking the NPY gene still respond to the effects of leptin suggesting 25 that it acts through other mechanisms independent of NPY (Erickson (1996) *Nature* 381: 415-421).

Although the discovery of leptin and its effect on obese 25 rodents has led to renewed interest in adipocyte biochemistry, the effect of leptin in human obesity is less well understood. In fact, there appears to be little correlation between obese rodents and obese humans, for example administration of leptin to obese patients has little 30 effect on body weight and also there have only been isolated accounts of ob-ob human equivalents (Montague et al., (1997) *Nature* 387: 903-908). Thus there remains much to be discovered regarding adipocyte biology and the mechanisms of obesity in humans.

35 One area of adipocyte biology that is relatively

uncharacterised is the adipocyte cell surface. Indeed, a more complete understanding of the proteins and receptors expressed on the adipocyte cell surface may provide a major insight into the causes of obesity. A few receptors have 5 already been identified on adipocytes, for example the insulin receptor, the leptin receptor and also several fatty acid transporters (Reed et al., (1977) PNAS 74(11): 4876-4880; Lefebvre et al., (1998) Diabetes 47: 98-103; Tartaglia et al., (1995) Cell 83: 1263-1271; Rosenbaum et al., (1997) 10 New Eng. J. Med. 337: 396-407; Hui and Bernlohr (1997) Frontiers in Bioscience 2: 222-231). In addition, up to 20% of the adipocyte cell surface is comprised of surface invaginations of the plasma membrane known as caveolae (Lisanti et al., (1994) Trends Cell Biol. 4: 231-235). These 15 structures are unique in that they are rich in signalling molecules and their cognate receptors, including G proteins, Src-like kinases, protein kinase C and Ras-related GTPases (Sargiacomo et al., (1993) J. Cell Biol. 122: 789-807; Lisanti et al., (1994) J. Cell Biol. 126: 111-126; Chun et 20 al., (1994) PNAS 91: 11728-11732; Chang et al., (1994) J. Cell Biol. 126: 127-138; Shenoy-Scaria et al., (1994) J. Cell Biol. 126: 353-363; Robbins et al., (1995) Mol. Cell Biol. 15: 3507-3515; Schnitzer et al., (1995) Science 269: 1435-1439). When one also remembers that adipocytes secrete many 25 soluble factors, for example leptin, TNF- α and adiponectin (Zhang et al., (1994) Nature 372: 425-432; Hotamisligil et al., (1993) Science 259: 87-91; Cook et al., (1985) PNAS 82: 6480-6484), it is clear that although adipocytes are a 30 metabolically active cell type, relatively little is known about their cell surface signalling mechanisms.

35 Adipocytes are a unique cell type in that they can store large quantities of lipid and it is likely that this phenotype is reflected in the enzyme and receptor composition of the plasma membrane. One approach that has been used to

further our knowledge of the adipocyte cell surface is the production of antibodies to plasma membrane antigens. Antibodies have proven to be highly useful research tools over the years due to the variety of techniques in which they 5 can be applied; for example Western blotting, immunocytochemistry, ELISA, immunoprecipitation, affinity chromatography to name but a few. This versatility has led to the use of antibodies in many characterisation studies, for example in the identification of disease and cell 10 differentiation/development markers. Thus, in effect, a panel of antibodies directed against adipocyte plasma membranes would be a toolkit with which to study adipocyte biology.

Anti-adipocyte antibodies have been generated by immunising 15 animals with adipocyte plasma membranes isolated from various species (rats, cattle and sheep) (Pillion et al., (1979) J. Biol Chem. 254: 3211-3220; Thompson et al., (1979) In Vitro 15: 441-445; Lee et al., (1986) J. Dev. Physiol. 8: 207-226; Cryer et al., (1984) J. Dev. Physiol. 6: 159-176; Nassar AH, 20 Thesis, Corvallis, OR: Oregon State University, 1989; Flint et al., (1986) Int. J. Obesity 10: 69-77). Although polyclonal sera have been used to identify adipocyte membrane 25 proteins, this approach is generally complicated by a number of factors, such as differing antibody affinities and isotypes, variability in serum samples and production of antibodies to intracellular epitopes. An alternative approach is to use monoclonal antibodies rather than 30 polyclonal antisera to study adipocyte membrane proteins (Killefer and Hu (1990) PSEBM 194: 172-176; Wright and Hausman (1995) Obesity Research 3: 265-272; De clercq et al., (1997) J. Anim. Sci. 75: 1791-1797).

To isolate antibodies from a phage library (McCafferty et al., (1990) Nature 348: 552-554; Johnson and Chiswell (1993) 35 Current Opinion in Structural Biology 3: 564-571; Winter et

al., (1994) Ann. Rev. Immunol. 12: 433-455), typical selection techniques involve immobilising a purified antigen on a solid support and then panning with the antibody library (Vaughan et al., (1996) Nature Biotechnology 14: 309-314).

5 Whilst this works well for purified antigens, selection procedures for more complex antigens are less well developed. Phage antibodies have been isolated to red blood cells, leukocytes, epithelial cells and tumor cells (Marks et al., (1993) Biotechnology 11: 1145-1149; De Kruif et al., (1995) PNAS 92: 3938-3942; Palmer et al., (1997) Immunology 91: 473-478; Watters et al., (1997) Immunotechnology 3: 21-29), but only limited selections have been described with regard to selections on antigenically complex targets such as the cell surface.

15 The present invention has arisen by provision of a panel of anti-adipocyte monoclonal antibodies binding to many different antigens on the adipocyte cell surface. The antibodies have been characterised by immunocytochemistry on 20 a panel of normal human tissues to establish tissue and cell type specificity and allow for antigens of interest to be characterised and subsequently identified. These anti-adipocyte antibodies may also be used in the treatment of obesity and obesity related diseases. One advantage of 25 this approach is that antibodies specific for different fat depots may be produced: for example, intra-abdominal fat is associated with many of the complications of obesity (NIDDM, hypertension, heart disease and colon cancer); alternatively recurrent lipoma (benign fatty tumours) may be controlled 30 using specific antibodies; other cardiovascular conditions associated with obesity such as atherosclerosis may be targeted; and more unusual conditions such as thyroid eye disease, where patients suffer from an increase in adipose mass around the eye-ball and is currently only treatable by 35 surgery. Antibodies may be used to deliver drugs or

pro-drugs directly to the fat mass of an obese patient or alternatively an antibody with an appropriate specificity may be used as a therapeutic itself. For example, antibodies binding specifically to adipocytes may be used to activate 5 the immune system to destroy the cells by complement mediated lysis (Marks et al., (1993) Biotechnology 11: 1145-1149; Wright and Hausman (1995) Obesity Research 3: 265-272; De clercq et al., (1997) J. Anim. Sci. 75: 1791-1797). Using 10 antibodies that can target adipocytes offers an alternative means of treatment for obese patients other than undergoing surgery to remove excess fat.

In one aspect, the present invention provides a library or panel of at least or about 10 different specific binding 15 members, the library or panel comprising specific binding members each able to bind whole adipocytes and each comprising an antibody VH variable domain, wherein each antibody VH variable domain comprises a VH CDR shown in Table 4 and optionally has an amino acid sequence selected from the 20 group consisting of those with a SEQ ID NO. listed in Table 5.

Such a library may include at least or about 20 different antibody VH CDR's or variable domains, or at least 50, 60, 25 70, 80, 90 or 100 different antibody VH CDR's or variable domains.

In one embodiment, the library contains all 108 different VH domains of which the amino acid SEQ ID NO.'s are listed in 30 Table 5. In another embodiment, the library contains all 108 different VH CDR3's shown in Table 4.

Generally, each VH domain is paired with a VL domain. The VL domain may be any selected from those disclosed herein, e.g. 35 with a SEQ ID NO. listed in Table 5. Preferred VL domains

for inclusion in a library or specific binding member according to the present invention include those with SEQ ID NO.'S 4, 8, 26, 84, 88 and 116, especially SEQ ID NO. 26 and SEQ ID NO. 84.

5

In a further aspect, the present invention provides a method of obtaining one or more specific binding members able to bind an adipocyte antigen, the method including bringing into contact a library of specific binding members according to 10 the invention and said adipocyte antigen, and selecting one or more specific binding members of the library able to bind said adipocyte antigen.

The library may be displayed on the surface of bacteriophage 15 particles, each particle containing nucleic acid encoding the antibody VH variable domain displayed on its surface, and optionally also a displayed VL domain if present.

Following selection of specific binding members able to bind 20 the antigen and displayed on bacteriophage particles, nucleic acid may be taken from a bacteriophage particle displaying a said selected specific binding member. Such nucleic acid may be used in subsequent production of a specific binding member or an antibody VH variable domain (optionally an antibody VL 25 variable domain) by expression from nucleic acid with the sequence of nucleic acid taken from a bacteriophage particle displaying a said selected specific binding member.

An antibody VH variable domain with the amino acid sequence 30 of an antibody VH variable domain of a said selected specific binding member may be provided in isolated form, as may a specific binding member comprising such a VH domain.

A plurality of antibody VH variable domains each with an 35 amino acid sequence of an antibody VH variable domain of a

said selected specific binding member may be provided in isolated form, as may a plurality of specific binding members comprising such VH domains.

5 A mixture of said plurality of antibody VH variable domains may be provided in isolated form.

An antibody VH variable domain with an amino acid sequence of an antibody VH variable domain of a said selected specific 10 binding member, a plurality of said antibody VH variable domains, or a mixture of a plurality of said antibody VH variable domains in isolated form may be formulated into a composition including at least one additional component, for instance a composition including a pharmaceutically 15 acceptable excipient. The same applies to specific binding members comprising a VH domain and optionally a VL domain, also pluralities and mixtures thereof.

The amino acid sequence of an antibody VH variable domain of 20 a said selected specific binding member may be provided in a fusion with additional amino acids.

As noted, the amino acid sequence of an antibody VH variable domain of a said selected specific binding member may be 25 provided in combination with an antibody VL variable domain thereby forming an antigen-binding site of an antibody.

The present invention further provides a mixture of 10 different specific binding members each comprising an 30 antibody VH variable domain, obtainable from a library as discussed, wherein each antibody VH variable domain has an amino acid sequence selected from the group consisting of the VH domains of Fat3, Fat13, Fat17, Fat31, Fat37, Fat40, Fat86, Fat97, Fat103 and Fat106 (SEQ ID NO.'s being given in Table 35 5).

In a still further aspect, the present invention further provides a mixture of 10 different specific binding members each comprising an antibody VH variable domain, obtainable from a library as discussed, wherein each antibody VH variable domain has an amino acid sequence comprising a CDR3 selected from the group consisting of the VH domains of Fat3, Fat13, Fat17, Fat31, Fat37, Fat40, Fat86, Fat97, Fat103 and Fat106 (the CDR3 sequences being shown in Table 4).

10 A composition may be provided in accordance with the present invention to comprise a plurality of different antibody VH variable domains obtainable from such a mixture.

Such a composition may include any one or more of the antibody VH variable domains of Fat3, Fat13, Fat17, Fat31, Fat37, Fat40, Fat86, Fat97, Fat103 and Fat106 (SEQ ID NO.'s being given in Table 5)

20 Such a composition preferably includes either or both of the antibody VH variable domains of Fat13 and Fat40.

In such a composition, one or more of said antibody VH variable domains may be in a fusion with additional amino acids.

25 In such a composition, one or more of said antibody VH variable domains may be in association with an antibody VL variable domain, preferably a VL domain disclosed herein.

30 In any VH/VL domain pairing of VH and VL domains disclosed herein, preferred embodiments include the pairings shown in Table 5.

35 In a further aspect, the present invention provides an antibody VH variable domain obtainable from a mixture or a

library as disclosed.

Such an antibody VH variable domain may have an amino acid sequence selected from the group consisting of those of Fat3, 5 Fat13, Fat17, Fat31, Fat37, Fat40, Fat86, Fat97, Fat103 and Fat106 (SEQ ID NO.'s being given in Table 5).

A further aspect of the present invention provides nucleic acid, generally isolated, encoding an antibody VH variable 10 domain and/or VL variable domain disclosed herein.

Another aspect of the present invention provides nucleic acid, generally isolated, encoding a VH CDR3 sequence disclosed herein.

15 A further aspect provides a host cell transformed with such nucleic acid.

A yet further aspect provides a method of production of an 20 antibody VH variable domain, the method including causing expression from encoding nucleic acid. Such a method may comprise culturing host cells under conditions for production of said antibody VH variable domain.

25 Analogous methods for production of VL variable domains and specific binding members comprising a VH and/or VL domain are provided as further aspects of the present invention.

30 A method of production may comprise a step of isolation and/or purification of the product.

A method of production may comprise formulating the product into a composition including at least one additional component, such as a pharmaceutically acceptable excipient.

Another aspect of the present invention provides a method of obtaining one or more antigen molecules, the method including bringing into contact material suspected of containing an antigen of interest and a specific binding member according to the invention, and selecting one or more antigen molecules bound by said specific binding member. The antigen of interest may, for example, be a specific marker, a molecule involved in fat metabolism, a receptor, a cytokine, an integrin or a signalling molecule.

10

Such a method may comprise bringing said material into contact with a plurality of specific binding members.

15 A selected antigen molecule may be provided in an isolated and/or purified form.

A said selected antigen molecule in isolated form may be formulated into a composition including at least one additional component.

20

A panel, library or mixture of specific binding members provided by the present invention is useful for selection of specific binding members against adipocytes and adipocyte antigens. An antibody panel may for example be used as an immunological tool in techniques such as ELISA, Western blotting, immunocytochemistry, immuno-precipitation and affinity chromatography.

30 A VH domain of which the sequence is disclosed herein may be combined with a VL domain of which the sequence is disclosed herein, or other VL domain, to provide a VH/VL pairing representing an antigen-binding site of an antibody. Similarly, a VL domain of which the sequence is disclosed herein may be combined with a VH domain of which the sequence 35 is disclosed herein, or other VH domain.

One or more CDRs may be taken from a VH or VL domain and incorporated into a suitable framework. This is discussed further below.

5 Variants of the VH and VL domains and CDRs of which the sequences are set out herein and which can be employed in specific binding members for adipocytes and adipocyte antigens can be obtained by means of methods of sequence alteration or mutation and screening. Such methods are also
10 provided by the present invention.

Variable domain amino acid sequence variants of any of the VH and VL domains whose sequences are specifically disclosed herein may be employed in accordance with the present
15 invention, as discussed. Particular variants may include one or more amino acid sequence alterations (addition, deletion, substitution and/or insertion of an amino acid residue), maybe less than about 20 alterations, less than about 15 alterations, less than about 10 alterations or less than
20 about 5 alterations, 4, 3, 2 or 1. Alterations may be made in one or more framework regions and/or one or more CDR's.

A specific binding member according to the invention may be one which competes for binding to antigen with any specific
25 binding member which both binds the antigen and comprises a specific binding member, VH and/or VL domain disclosed herein, or VH CDR3 disclosed herein, or variant of any of these. Competition between binding members may be assayed easily *in vitro*, for example using ELISA and/or by tagging a
30 specific reporter molecule to one binding member which can be detected in the presence of other untagged binding member(s), to enable identification of specific binding members which bind the same epitope or an overlapping epitope.

35 In addition to antibody sequences, the specific binding

member may comprise other amino acids, e.g. forming a peptide or polypeptide, such as a folded domain, or to impart to the molecule another functional characteristic in addition to ability to bind antigen. Specific binding members of the 5 invention may carry a detectable label, or may be conjugated to a toxin or enzyme (e.g. via a peptidyl bond or linker).

A further aspect of the present invention provides a method of obtaining one or more specific binding members with a 10 desired property, the method including bringing into contact a library or panel of specific binding members and selecting one or more with the desired property. Such a method may employ phage display technology, wherein the specific binding members in the library or panel are displayed on the surface 15 of bacteriophage particles, each particle containing nucleic acid encoding the specific binding member or a component thereof (e.g. VH domain). Nucleic acid may be taken from a bacteriophage particle containing nucleic acid encoding a selected specific binding member or component thereof, and 20 nucleic acid with the sequence of the nucleic acid from the particle can be used to provide (by means of recombinant technology) the encoded product, or further nucleic acid with the sequence, or a variant or derivative.

25 In further aspects, the invention provides an isolated nucleic acid which comprises a sequence encoding a specific binding member as defined above, and methods of preparing specific binding members of the invention which comprise expressing said nucleic acids under conditions to bring about 30 expression of said binding member, and recovering the binding member.

35 Specific binding members according to the invention may be used in a method of treatment or diagnosis of the human or animal body, such as a method of treatment (which may include

prophylactic treatment) of a disease or disorder in a human patient which comprises administering to said patient an effective amount of a specific binding member of the invention. Conditions treatable in accordance with the 5 present invention include obesity and obesity related disorders, as disclosed herein.

These and other aspects of the invention are described in further detail below.

10

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows results of ELISA experiments with the antibody VH/VL pairing of Fat 37 on various adipocyte plasma membranes 15 from each of the indicated adipose depots.

Figure 2 shows optical densities of various antibody VH/VL pairings measured at different temperatures, as a measure of stability.

20

TERMINOLOGY

Specific binding member

This describes a member of a pair of molecules which have 25 binding specificity for one another. The members of a specific binding pair may be naturally derived or wholly or partially synthetically produced. One member of the pair of molecules has an area on its surface, or a cavity, which specifically binds to and is therefore complementary to a 30 particular spatial and polar organisation of the other member of the pair of molecules. Thus the members of the pair have the property of binding specifically to each other. Examples of types of specific binding pairs are antigen-antibody, biotin-avidin, hormone-hormone receptor, receptor-ligand, 35 enzyme-substrate. This application is concerned with

antigen-antibody type reactions.

Antibody

This describes an immunoglobulin whether natural or partly or
5 wholly synthetically produced. The term also covers any
polypeptide or protein having a binding domain which is, or
is substantially homologous to, an antibody binding domain.
These can be derived from natural sources, or they may be
partly or wholly synthetically produced. Examples of
10 antibodies are the immunoglobulin isotypes and their isotypic
subclasses; fragments which comprise an antigen binding
domain such as Fab, scFv, Fv, dAb, Fd; and diabodies.

It is possible to take monoclonal and other antibodies and
15 use techniques of recombinant DNA technology to produce other
antibodies or chimeric molecules which retain the specificity
of the original antibody. Such techniques may involve
introducing DNA encoding the immunoglobulin variable region,
or the complementarity determining regions (CDRs), of an
20 antibody to the constant regions, or constant regions plus
framework regions, of a different immunoglobulin. See, for
instance, EP-A-184187, GB 2188638A or EP-A-239400. A
hybridoma or other cell producing an antibody may be subject
25 to genetic mutation or other changes, which may or may not
alter the binding specificity of antibodies produced.

As antibodies can be modified in a number of ways, the term
"antibody" should be construed as covering any specific
binding member or substance having a binding domain with the
30 required specificity. Thus, this term covers antibody
fragments, derivatives, functional equivalents and homologues
of antibodies, including any polypeptide comprising an
immunoglobulin binding domain, whether natural or wholly or
partially synthetic. Chimeric molecules comprising an
35 immunoglobulin binding domain, or equivalent, fused to

another polypeptide are therefore included. Cloning and expression of chimeric antibodies are described in EP-A-0120694 and EP-A-0125023.

5 It has been shown that fragments of a whole antibody can perform the function of binding antigens. Examples of binding fragments are (i) the Fab fragment consisting of VL, VH, CL and CH1 domains; (ii) the Fd fragment consisting of the VH and CH1 domains; (iii) the Fv fragment consisting of the VL and VH domains of a single antibody; (iv) the dAb fragment (Ward, E.S. et al., *Nature* 341, 544-546 (1989)) which consists of a VH domain; (v) isolated CDR regions; (vi) F(ab')2 fragments, a bivalent fragment comprising two linked Fab fragments (vii) single chain Fv molecules (scFv), wherein 10 a VH domain and a VL domain are linked by a peptide linker which allows the two domains to associate to form an antigen binding site (Bird et al, *Science*, **242**, 423-426, 1988; Huston et al, *PNAS USA*, **85**, 5879-5883, 1988); (viii) bispecific 15 single chain Fv dimers (PCT/US92/09965) and (ix) "diabodies", multivalent or multispecific fragments constructed by gene 20 fusion (WO94/13804; P. Holliger et al, *Proc. Natl. Acad. Sci. USA* **90** 6444-6448, 1993). Fv, scFv or diabody molecules may be stabilised by the incorporation of disulphide bridges 25 linking the VH and VL domains (Y. Reiter et al, *Nature Biotech.*, **14**, 1239-1245, 1996). Minibodies comprising a scFv joined to a CH3 domain may also be made (S. Hu et al, *Cancer Res.*, **56**, 3055-3061, 1996).

30 Diabodies are multimers of polypeptides, each polypeptide comprising a first domain comprising a binding region of an immunoglobulin light chain and a second domain comprising a binding region of an immunoglobulin heavy chain, the two domains being linked (e.g. by a peptide linker) but unable to associate with each other to form an antigen binding site:

antigen binding sites are formed by the association of the first domain of one polypeptide within the multimer with the second domain of another polypeptide within the multimer (WO94/13804).

5

Where bispecific antibodies are to be used, these may be conventional bispecific antibodies, which can be manufactured in a variety of ways (Holliger, P. and Winter G. Current Opinion Biotechnol. **4**, 446-449 (1993)), e.g. prepared chemically or from hybrid hybridomas, or may be any of the bispecific antibody fragments mentioned above. It may be preferable to use scFv dimers or diabodies rather than whole antibodies. Diabodies and scFv can be constructed without an Fc region, using only variable domains, potentially reducing the effects of anti-idiotypic reaction.

Bispecific diabodies, as opposed to bispecific whole antibodies, may also be particularly useful because they can be readily constructed and expressed in *E.coli*. Diabodies (and many other polypeptides such as antibody fragments) of appropriate binding specificities can be readily selected using phage display (WO94/13804) from libraries. If one arm of the diabody is to be kept constant, for instance, with a specificity directed against antigen X, then a library can be made where the other arm is varied and an antibody of appropriate specificity selected. Bispecific whole antibodies may be made by knobs-into-holes engineering (J. B. B. Ridgeway et al, Protein Eng., **9**, 616-621, 1996).

30 *Antigen binding domain*

This describes the part of an antibody which comprises the area which specifically binds to and is complementary to part or all of an antigen. Where an antigen is large, an antibody may only bind to a particular part of the antigen, which part is termed an epitope. An antigen binding domain may be

provided by one or more antibody variable domains (e.g. a so-called Fd antibody fragment consisting of a VH domain).

Preferably, an antigen binding domain comprises an antibody light chain variable region (VL) and an antibody heavy chain variable region (VH).

Specific

This may be used to refer to the situation in which one member of a specific binding pair will not show any significant binding to molecules other than its specific binding partner(s). The term is also applicable where e.g. an antigen binding domain is specific for a particular epitope which is carried by a number of antigens, in which case the specific binding member carrying the antigen binding domain will be able to bind to the various antigens carrying the epitope.

Comprise

This is generally used in the sense of include, that is to say permitting the presence of one or more features or components.

Isolated

This refers to the state in which specific binding members of the invention, or nucleic acid encoding such binding members, will be in accordance with the present invention. Members and nucleic acid will be free or substantially free of material with which they are naturally associated such as other polypeptides or nucleic acids with which they are found in their natural environment, or the environment in which they are prepared (e.g. cell culture) when such preparation is by recombinant DNA technology practised *in vitro* or *in vivo*. Members and nucleic acid may be formulated with diluents or adjuvants and still for practical purposes be isolated - for example the members will normally be mixed

with gelatin or other carriers if used to coat microtitre plates for use in immunoassays, or will be mixed with pharmaceutically acceptable carriers or diluents when used in diagnosis or therapy. Specific binding members may be 5 glycosylated, either naturally or by systems of heterologous eukaryotic cells (e.g. CHO or NS0 (ECACC 85110503) cells), or they may be (for example if produced by expression in a prokaryotic cell) unglycosylated.

10 By "substantially as set out" it is meant that the relevant CDR or VH or VL domain of the invention will be either identical or highly similar to the specified regions of which the sequence is set out herein. By "highly similar" it is contemplated that from 1 to 5, preferably from 1 to 4 such as 15 1 to 3 or 1 or 2, or 3 or 4, substitutions may be made in the CDR and/or VH or VL domain.

20 The structure for carrying a CDR of the invention will generally be of an antibody heavy or light chain sequence or substantial portion thereof in which the CDR is located at a 25 location corresponding to the CDR of naturally occurring VH and VL antibody variable domains encoded by rearranged immunoglobulin genes. The structures and locations of immunoglobulin variable domains may be determined by reference to (Kabat, E.A. et al, Sequences of Proteins of Immunological Interest. 4th Edition. US Department of Health and Human Services. 1987, and updates thereof, now available on the Internet (<http://immuno.bme.nwu.edu>)).

30 Preferably, a CDR amino acid sequence substantially as set 35 out herein is carried as a CDR in a human variable domain or a substantial portion thereof. The VH CDR3 sequences substantially as set out herein represent preferred embodiments of the present invention and it is preferred that each of these is carried as a VH CDR3 in a human heavy chain

variable domain or a substantial portion thereof.

Variable domains employed in the invention may be derived from any germline or rearranged human variable domain, or may 5 be a synthetic variable domain based on consensus sequences of known human variable domains. A CDR-derived sequence or sequences of the invention (e.g. CDR3) may be introduced into a repertoire of variable domains lacking a CDR (e.g. CDR3), using recombinant DNA technology.

10

For example, Marks *et al* (*Bio/Technology*, 1992, 10:779-783) describe methods of producing repertoires of antibody variable domains in which consensus primers directed at or adjacent to the 5' end of the variable domain area are used 15 in conjunction with consensus primers to the third framework region of human VH genes to provide a repertoire of VH variable domains lacking a CDR3. Marks *et al* further describe how this repertoire may be combined with a CDR3 of a particular antibody. Using analogous techniques, the CDR3-derived sequences of the present invention may be shuffled 20 with repertoires of VH or VL domains lacking a CDR3, and the shuffled complete VH or VL domains combined with a cognate VL or VH domain to provide specific binding members of the invention. The repertoire may then be displayed in a 25 suitable host system such as the phage display system of WO92/01047 so that suitable specific binding members may be selected. A repertoire may consist of from anything from 10^4 individual members upwards, for example from 10^6 to 10^8 or 10^{10} members.

30

Analogous shuffling or combinatorial techniques are also disclosed by Stemmer (*Nature*, 1994, 370:389-391), who describes the technique in relation to a β -lactamase gene but observes that the approach may be used for the generation of 35 antibodies.

A further alternative is to generate novel VH or VL regions carrying a CDR-derived sequence or sequences of the invention using random mutagenesis of one or more selected VH and/or VL genes to generate mutations within the entire variable 5 domain. Such a technique is described by Gram *et al* (1992, *Proc. Natl. Acad. Sci., USA*, 89:3576-3580), who used error-prone PCR.

Another method which may be used is to direct mutagenesis to 10 CDR regions of VH or VL genes. Such techniques are disclosed by Barbas *et al*, (1994, *Proc. Natl. Acad. Sci., USA*, 91:3809-3813) and Schier *et al* (1996, *J. Mol. Biol.* 263:551-567).

All the above described techniques are known as such in the 15 art and in themselves do not form part of the present invention. The skilled person will be able to use such techniques to provide specific binding members of the invention using routine methodology in the art.

20 A further aspect of the invention provides a method for obtaining an antibody antigen binding domain specific for an adipocyte antigen, the method comprising providing by way of addition, deletion, substitution or insertion of one or more amino acids in the amino acid sequence of a VH domain set out 25 herein a VH domain which is an amino acid sequence variant of the VH domain, combining the VH domain thus provided with one or more VL domains, and testing the VH/VL combination or combinations for to identify an antibody antigen binding domain specific for an adipocyte antigen and optionally with 30 one or more of preferred properties. Said VL domain may have an amino acid sequence which is substantially as set out herein.

An analogous method may be employed in which one or more 35 sequence variants of a VL domain disclosed herein are

combined with one or more VH domains.

A further aspect of the invention provides a method of preparing a specific binding member specific for an adipocyte antigen, which method comprises:

(a) providing a starting repertoire of nucleic acids encoding a VH domain which either include a CDR3 to be replaced or lack a CDR3 encoding region;

(b) combining said repertoire with a donor nucleic acid encoding an amino acid sequence substantially as set out herein for a VH CDR3 such that said donor nucleic acid is inserted into the CDR3 region in the repertoire, so as to provide a product repertoire of nucleic acids encoding a VH domain;

(c) expressing the nucleic acids of said product repertoire;

(d) selecting a specific binding member specific for an adipocyte antigen; and

(e) recovering said specific binding member or nucleic acid encoding it.

Again, an analogous method may be employed in which a VL CDR3 of the invention is combined with a repertoire of nucleic acids encoding a VL domain which either include a CDR3 to be replaced or lack a CDR3 encoding region.

Similarly, one or more, or all three CDRs may be grafted into a repertoire of VH or VL domains which are then screened for a specific binding member or specific binding members specific for an adipocyte antigen.

A substantial portion of an immunoglobulin variable domain will comprise at least the three CDR regions, together with their intervening framework regions. Preferably, the portion will also include at least about 50% of either or both of the

first and fourth framework regions, the 50% being the C-terminal 50% of the first framework region and the N-terminal 50% of the fourth framework region. Additional residues at the N-terminal or C-terminal end of the substantial part of 5 the variable domain may be those not normally associated with naturally occurring variable domain regions. For example, construction of specific binding members of the present invention made by recombinant DNA techniques may result in the introduction of N- or C-terminal residues encoded by 10 linkers introduced to facilitate cloning or other manipulation steps. Other manipulation steps include the introduction of linkers to join variable domains of the invention to further protein sequences including immunoglobulin heavy chains, other variable domains (for 15 example in the production of diabodies) or protein labels as discussed in more details below.

Although in a preferred aspect of the invention specific binding members comprising a pair of VH and VL domains are 20 preferred, single binding domains based on either VH or VL domain sequences form further aspects of the invention. It is known that single immunoglobulin domains, especially VH domains, are capable of binding target antigens in a specific manner.

25 In the case of either of the single chain specific binding domains, these domains may be used to screen for complementary domains capable of forming a two-domain specific binding member able to bind an adipocyte antigen.

30 This may be achieved by phage display screening methods using the so-called hierarchical dual combinatorial approach as disclosed in WO 92/01047 in which an individual colony containing either an H or L chain clone is used to infect a 35 complete library of clones encoding the other chain (L or H)

and the resulting two-chain specific binding member is selected in accordance with phage display techniques such as those described in that reference. This technique is also disclosed in Marks *et al*, *ibid*.

5

Specific binding members of the present invention may further comprise antibody constant regions or parts thereof. For example, a VL domain may be attached at its C-terminal end to antibody light chain constant domains including human C κ or 10 C λ chains, preferably C λ chains. Similarly, a specific binding member based on a VH domain may be attached at its C-terminal end to all or part of an immunoglobulin heavy chain derived from any antibody isotype, e.g. IgG, IgA, IgE and IgM and any of the isotype sub-classes, particularly IgG1 and 15 IgG4. IgG4 is preferred.

Antibodies of the invention may be labelled with a detectable or functional label. Detectable labels include radiolabels such as ^{131}I or ^{99}Tc , which may be attached to antibodies of the 20 invention using conventional chemistry known in the art of antibody imaging. Labels also include enzyme labels such as horseradish peroxidase. Labels further include chemical moieties such as biotin which may be detected via binding to a specific cognate detectable moiety, e.g. labelled avidin.

25

Antibodies of the present invention are designed to be used in methods of diagnosis or treatment in human or animal subjects, preferably human.

30 Accordingly, further aspects of the invention provide methods of treatment comprising administration of a specific binding member as provided, pharmaceutical compositions comprising such a specific binding member, and use of such a specific binding member in the manufacture of a medicament for 35 administration, for example in a method of making a

medicament or pharmaceutical composition comprising formulating the specific binding member with a pharmaceutically acceptable excipient.

5 In accordance with the present invention, compositions provided may be administered to individuals. Administration is preferably in a "therapeutically effective amount", this being sufficient to show benefit to a patient. Such benefit may be at least amelioration of at least one symptom. The
10 actual amount administered, and rate and time-course of administration, will depend on the nature and severity of what is being treated. Prescription of treatment, eg decisions on dosage etc, is within the responsibility of general practitioners and other medical doctors. Appropriate
15 doses of antibody are well known in the art; see Ledermann J.A. et al. (1991) Int J. Cancer 47: 659-664; Bagshawe K.D. et al. (1991) Antibody, Immunoconjugates and Radiopharmaceuticals 4: 915-922.

20 A composition may be administered alone or in combination with other treatments, either simultaneously or sequentially dependent upon the condition to be treated.

25 Antibodies of the present invention may be administered to a patient in need of treatment via any suitable route, usually by injection into the bloodstream or directly into the site to be treated, e.g. cornea or wound. The precise dose will depend upon a number of factors, including whether the antibody is for diagnosis or for treatment, the size and
30 location of the area to be treated (e.g. wound), the precise nature of the antibody (e.g. whole antibody, fragment or diabody), and the nature of any detectable label or other molecule attached to the antibody. A typical antibody dose will be in the range 0.5mg to 100g for systemic applications, and 10 μ g to 1mg for local applications. Typically, the
35

antibody will be a whole antibody, preferably the IgG4 isotype. This is a dose for a single treatment of an adult patient, which may be proportionally adjusted for children and infants, and also adjusted for other antibody formats in proportion to molecular weight. Treatments may be repeated at daily, twice-weekly, weekly or monthly intervals, at the discretion of the physician.

It is presently preferred that a whole antibody of the IgG4 isotype is used for systemic and local applications but for local applications a scFv antibody may be particularly valuable.

Specific binding members of the present invention will usually be administered in the form of a pharmaceutical composition, which may comprise at least one component in addition to the specific binding member.

Thus pharmaceutical compositions according to the present invention, and for use in accordance with the present invention, may comprise, in addition to active ingredient, a pharmaceutically acceptable excipient, carrier, buffer, stabiliser or other materials well known to those skilled in the art. Such materials should be non-toxic and should not interfere with the efficacy of the active ingredient. The precise nature of the carrier or other material will depend on the route of administration, which may be oral, or by injection, e.g. intravenous.

Pharmaceutical compositions for oral administration may be in tablet, capsule, powder or liquid form. A tablet may comprise a solid carrier such as gelatin or an adjuvant. Liquid pharmaceutical compositions generally comprise a liquid carrier such as water, petroleum, animal or vegetable oils, mineral oil or synthetic oil. Physiological saline

solution, dextrose or other saccharide solution or glycols such as ethylene glycol, propylene glycol or polyethylene glycol may be included.

5 For intravenous, injection, or injection at the site of affliction, the active ingredient will be in the form of a parenterally acceptable aqueous solution which is pyrogen-free and has suitable pH, isotonicity and stability. Those of relevant skill in the art are well able to prepare
10 suitable solutions using, for example, isotonic vehicles such as Sodium Chloride Injection, Ringer's Injection, Lactated Ringer's Injection. Preservatives, stabilisers, buffers, antioxidants and/or other additives may be included, as required.

15 A composition may be administered alone or in combination with other treatments, either simultaneously or sequentially dependent upon the condition to be treated. Other treatments may include the administration of suitable doses of pain
20 relief drugs such as non-steroidal anti-inflammatory drugs (e.g. aspirin, paracetamol, ibuprofen or ketoprofen) or opiates such as morphine, or anti-emetics.

25 The present invention provides a method comprising causing or allowing binding of a specific binding member as provided herein to an adipocyte antigen. As noted, such binding may take place *in vivo*, e.g. following administration of a specific binding member, or nucleic acid encoding a specific binding member, or it may take place *in vitro*, for example in
30 ELISA, Western blotting, immunocytochemistry, immuno-precipitation or affinity chromatography.

35 The amount of binding of specific binding member to an adipocyte antigen may be determined. Quantitation may be related to the amount of the antigen in a test sample, which

may be of diagnostic interest.

The reactivities of antibodies on a sample may be determined by any appropriate means. Radioimmunoassay (RIA) is one

5 possibility. Radioactive labelled antigen is mixed with unlabelled antigen (the test sample) and allowed to bind to the antibody. Bound antigen is physically separated from unbound antigen and the amount of radioactive antigen bound to the antibody determined. The more antigen there is in the 10 test sample the less radioactive antigen will bind to the antibody. A competitive binding assay may also be used with non-radioactive antigen, using antigen or an analogue linked to a reporter molecule. The reporter molecule may be a 15 fluorochrome, phosphor or laser dye with spectrally isolated absorption or emission characteristics. Suitable fluorochromes include fluorescein, rhodamine, phycoerythrin and Texas Red. Suitable chromogenic dyes include diaminobenzidine.

20 Other reporters include macromolecular colloidal particles or particulate material such as latex beads that are coloured, magnetic or paramagnetic, and biologically or chemically active agents that can directly or indirectly cause detectable signals to be visually observed, electronically

25 detected or otherwise recorded. These molecules may be enzymes which catalyse reactions that develop or change colours or cause changes in electrical properties, for example. They may be molecularly excitable, such that electronic transitions between energy states result in

30 characteristic spectral absorptions or emissions. They may include chemical entities used in conjunction with biosensors. Biotin/avidin or biotin/streptavidin and alkaline phosphatase detection systems may be employed.

35 The signals generated by individual antibody-reporter

conjugates may be used to derive quantifiable absolute or relative data of the relevant antibody binding in samples (normal and test).

5 The present invention also provides the use of a specific binding member as above for measuring antigen levels in a competition assay, that is to say a method of measuring the level of antigen in a sample by employing a specific binding member as provided by the present invention in a competition assay. This may be where the physical separation of bound from unbound antigen is not required. Linking a reporter molecule to the specific binding member so that a physical or optical change occurs on binding is one possibility. The reporter molecule may directly or indirectly generate 10 detectable, and preferably measurable, signals. The linkage of reporter molecules may be directly or indirectly, covalently, e.g. via a peptide bond or non-covalently. Linkage via a peptide bond may be as a result of recombinant 15 expression of a gene fusion encoding antibody and reporter molecule.

20

The present invention also provides for measuring levels of antigen directly, by employing a specific binding member according to the invention for example in a biosensor system.

25 The mode of determining binding is not a feature of the present invention and those skilled in the art are able to choose a suitable mode according to their preference and general knowledge.

30 As noted, an adipocyte antigen may be on the surface of an adipocyte. Accordingly, methods of detection and determination of the presence or level of adipocyte antigen, and other methods and uses herein, encompass such methods 35 when used to detect or determine the presence or level of

adipocytes, for example in a cell or tissue sample, except where context requires otherwise.

The present invention further extends to a specific binding member which competes for binding to an adipocyte antigen with any specific binding member which both binds the antigen and comprises a V domain including a CDR with amino acid sequence substantially as set out herein or a V domain with amino acid sequence substantially as set out herein.

Competition between binding members may be assayed easily *in vitro*, for example by tagging a specific reporter molecule to one binding member which can be detected in the presence of other untagged binding member(s), to enable identification of specific binding members which bind the same epitope or an overlapping epitope. Competition may be determined for example using the ELISA as described in Example 5 or Example 7.

In testing for competition a peptide fragment of the antigen may be employed, especially a peptide including an epitope of interest. A peptide may have the epitope sequence plus one or more amino acids at either end, may be used. Such a peptide may be said to "consist essentially" of the specified sequence. Specific binding members according to the present invention may be such that their binding for antigen is inhibited by a peptide with or including the sequence given. In testing for this, a peptide with either sequence plus one or more amino acids may be used.

Specific binding members which bind a specific peptide may be isolated for example from a phage display library by panning with the peptide(s).

The present invention further provides an isolated nucleic acid encoding a specific binding member of the present

invention. Nucleic acid includes DNA and RNA. In a preferred aspect, the present invention provides a nucleic acid which codes for a CDR or VH or VL domain of the invention as defined above.

5

The present invention also provides constructs in the form of plasmids, vectors, transcription or expression cassettes which comprise at least one polynucleotide as above.

10 The present invention also provides a recombinant host cell which comprises one or more constructs as above. A nucleic acid encoding any CDR, VH or VL domain, or specific binding member as provided itself forms an aspect of the present invention, as does a method of production of the encoded product, which method comprises expression from encoding nucleic acid therefor. Expression may conveniently be achieved by culturing under appropriate conditions recombinant host cells containing the nucleic acid.

15 Following production by expression of a VH or VL domain, or specific binding member may be isolated and/or purified using any suitable technique, then used as appropriate.

20 Specific binding members, VH and/or VL domains, and encoding nucleic acid molecules and vectors according to the present invention may be provided isolated and/or purified, e.g. from their natural environment, in substantially pure or homogeneous form, or, in the case of nucleic acid, free or substantially free of nucleic acid or genes other than the sequence encoding a polypeptide with the required function.

25 Nucleic acid according to the present invention may comprise DNA or RNA and may be wholly or partially synthetic. Reference to a nucleotide sequence as set out herein encompasses a DNA molecule with the specified sequence, and encompasses a RNA molecule with the specified sequence in which U is substituted for T, unless context requires

otherwise.

Systems for cloning and expression of a polypeptide in a variety of different host cells are well known. Suitable 5 host cells include bacteria, mammalian cells, yeast and baculovirus systems. Mammalian cell lines available in the art for expression of a heterologous polypeptide include Chinese hamster ovary cells, HeLa cells, baby hamster kidney cells, NSO mouse melanoma cells and many others. A common, 10 preferred bacterial host is *E. coli*.

The expression of antibodies and antibody fragments in prokaryotic cells such as *E. coli* is well established in the art. For a review, see for example Plückthun, A. 15 Bio/Technology **9**: 545-551 (1991). Expression in eukaryotic cells in culture is also available to those skilled in the art as an option for production of a specific binding member, see for recent reviews, for example Ref, M.E. (1993) Curr. Opinion Biotech. **4**: 573-576; Trill J.J. et al. (1995) Curr. 20 Opinion Biotech **6**: 553-560.

Suitable vectors can be chosen or constructed, containing appropriate regulatory sequences, including promoter sequences, terminator sequences, polyadenylation sequences, 25 enhancer sequences, marker genes and other sequences as appropriate. Vectors may be plasmids, viral e.g. 'phage, or phagemid, as appropriate. For further details see, for example, *Molecular Cloning: a Laboratory Manual*: 2nd edition, Sambrook et al., 1989, Cold Spring Harbor Laboratory Press. 30 Many known techniques and protocols for manipulation of nucleic acid, for example in preparation of nucleic acid constructs, mutagenesis, sequencing, introduction of DNA into cells and gene expression, and analysis of proteins, are described in detail in *Short Protocols in Molecular Biology*,

Second Edition, Ausubel et al. eds., John Wiley & Sons, 1992. The disclosures of Sambrook et al. and Ausubel et al. are incorporated herein by reference.

5 Thus, a further aspect of the present invention provides a host cell containing nucleic acid as disclosed herein. A still further aspect provides a method comprising introducing such nucleic acid into a host cell. The introduction may employ any available technique. For eukaryotic cells, 10 suitable techniques may include calcium phosphate transfection, DEAE-Dextran, electroporation, liposome-mediated transfection and transduction using retrovirus or other virus, e.g. vaccinia or, for insect cells, baculovirus. For bacterial cells, suitable techniques may include calcium 15 chloride transformation, electroporation and transfection using bacteriophage.

The introduction may be followed by causing or allowing expression from the nucleic acid, e.g. by culturing host 20 cells under conditions for expression of the gene.

In one embodiment, the nucleic acid of the invention is integrated into the genome (e.g. chromosome) of the host cell. Integration may be promoted by inclusion of sequences 25 which promote recombination with the genome, in accordance with standard techniques.

The present invention also provides a method which comprises using a construct as stated above in an expression system in 30 order to express a specific binding member or polypeptide as above.

Aspects and embodiments of the present invention will now be illustrated by way of example with reference to the following 35 experimentation.

LIST OF EXAMPLES

EXAMPLE 1: Preparation Of Adipocytes From Human Adipose Tissue And Isolation Of A Plasma Membrane Rich Fraction.

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EXAMPLE 2: Selection Of Antibody-Expressing Phage by Panning on Isolated Adipocytes and Adipocyte Plasma Membranes.

EXAMPLE 3: Selection Of Antibody-Expressing Phage by Panning on Intact Adipose Tissue.

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EXAMPLE 4: ProxiMol Selection Of Antibody-Expressing Phage Using An Anti-Adipocyte Polyclonal Serum As The Targeting Reagent.

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EXAMPLE 5: Identification & Characterisation Of Selected Antibodies By Adipocyte Plasma Membrane ELISA And DNA Sequencing.

EXAMPLE 6: Characterisation Of Anti-Adipocyte Antibodies By Immunocytochemistry On Human Tissues.

20

EXAMPLE 7: Characterisation Of Antigens Recognised By The Anti-Adipocyte Antibodies.

25

ABBREVIATIONS

Immunocytochemistry (ICC)

Enzyme linked immunosorbent assay (ELISA)

30 Bovine serum albumin (BSA)

Horseradish peroxidase (HRP)

Bacterial growth medium (2TY: 16g Bacto-tryptone, 10g Yeast extract and 5g NaCl per litre of distilled water)

35 Bacterial growth medium (2TYAG: 2TY supplemented with 100mg/ml ampicillin and 2% glucose)

Bacterial growth medium (2TYAK: 2TY supplemented with 100mg/ml ampicillin and 50mg/ml kanamycin)

Phosphate Buffered Saline (PBS)

Phosphate Buffered Saline + 0.1% (v/v) Tween 20 (PBST)

5 Triethylamine (TEA)

Multiplicity of Infection (MOI)

Immobilised Metal Affinity Chromatography (IMAC)

Polyacrylamide Gel Electrophoresis (PAGE)

Isoelectric Focusing (IEF)

10 Polymerase Chain Reaction (PCR)

Polyvinylidene Difluoride (PVDF)

3,3',5,5'-Tetramethyl Benzidine (TMB)

N-Hydroxysuccinimide (NHS)

Critical micelle concentration (CMC)

15 Sodium dodecyl sulphate (SDS)

Surface-enhanced laser desorption/ionization (SELDI mass spectrometry)

EXAMPLE 1: PREPARATION OF ADIPOCYTES FROM HUMAN ADIPOSE

20 *TISSUE AND ISOLATION OF A PLASMA MEMBRANE RICH FRACTION*

1.1 Sources of adipose tissue.

Normal human adipose tissue was obtained from a number of depots from both male & female patients, aged between 24-79:

25 breast, abdomen, thigh, omental (also known as visceral or intraperitoneal adipose), back, arm, eye and lipoma (fatty tumour tissue). Depending on the nature of the surgery involved, the amount of fat obtained ranged from a couple of grams to over 1kg. All adipose samples were treated in an identical manner.

1.2 Preparation of adipocytes.

Adipocytes were prepared from intact adipose as described by Kestin (J. Anim. Sci., 71, 1486-94, 1993). Up to 100g of

35 adipose tissue was minced with scissors until the pieces were

less than 5mm³ in size. This minced adipose tissue was then mixed with prewarmed (37°C) medium 199 (2 vols/wt), 3% BSA (w/v) (Fatty acid free, Boehringer 775835) and 1mg/ml collagenase (Sigma C-6885) and incubated at 37°C with shaking at 120rpm for between 30-60 mins. The reaction was deemed complete when the majority of the adipose tissue pieces had been digested and a layer of adipocytes could be seen floating on the surface of the medium.

5 To remove undigested tissue, the reaction mix was diluted 5:1 (v/v) with prewarmed medium 199 and sieved (0.25µm pore size) into a fresh beaker. Viable adipocytes were allowed to float to the surface and the medium aspirated from beneath the cells. A further 3 volumes of prewarmed medium 199 was added 10 to the cells which were resuspended by gentle swirling. Adipocytes were once again allowed to float and the medium removed from beneath the cells. This washing procedure was then continued until the wash media beneath the cells 15 appeared clear, usually after 3-5 washes. Cells were then taken directly for selections (see Example 2), otherwise unused cells were mixed (1:1 v/v) with 12mM Tris, 0.25M sucrose, pH 7.5 and stored frozen at -70°C for preparation of 20 plasma membranes.

25 *1.3 Preparation of a plasma membrane rich fraction from adipocytes*
Adipocytes frozen at -70°C in 12mM Tris, 0.25M sucrose, pH 7.5 were thawed to room temperature. To ensure complete cell lysis, the adipocytes were once again frozen in dry ice and 30 thawed to room temperature. The adipocytes were then centrifuged at 3000rpm for 2 minutes at room temperature. Following this step, the lysed adipocytes will partition in a test tube with a pellet of ruptured cells and cell debris at the bottom, under a layer of infranatant above which is a 35 layer of intact adipocytes under a layer of clear lipid.

Tubes were placed on ice until the lipid layer had solidified. The infranatant, which contains the plasma membrane fraction, was pipetted into a fresh tube and then subjected to a series of centrifugations at 4°C. A nuclear fraction was recovered at 270xg for 10 minutes and the supernatant centrifuged for 10 minutes at 8000xg for the recovery of a mitochondrial and lysosomal fraction. The plasma membrane fraction was subsequently recovered by centrifugation at 104,000xg for 60 minutes from the post mitochondrial supernatant, resuspended in PBS and frozen at -70°C until used. Total protein concentration of the membrane fraction was determined using the Bradford assay reagent (Pierce 500-0006).

15 *1.4 Summary*

Human adipose tissue was obtained from a number of depots. Isolation of adipocytes from these tissues was performed rapidly, with viable cells being identified as the population of cells floating at the surface of the tissue homogenate. Once isolated, the floating adipocytes pack together at approximately 2×10^6 cells/ml and from 100g of adipose approximately 500mls or 1×10^9 adipocytes could be isolated. These adipocytes were extensively washed and 50µl or 1×10^5 cells used directly in selections (see Example 2). The remaining adipocytes were used to prepare plasma membranes. For a typical preparation, 50ml or 1×10^8 adipocytes yielded around 1mg of plasma membranes in 0.5ml PBS. These plasma membranes were then used in further selections or for screening the anti-adipocyte antibodies by ELISA.

30

EXAMPLE 2: SELECTION OF ANTIBODY-EXPRESSING PHAGE BY PANNING ON ISOLATED ADIPOCYTES AND ADIPOCYTE PLASMA MEMBRANES

2.1 Antibody repertoire

35 A Large single chain Fv library derived from lymphoid tissues

including tonsil, bone marrow and peripheral blood lymphocytes (Vaughan et al, *Nature Biotechnology*, 14, 309-314, 1996) was used for all selections.

5 Polyadenylated RNA was prepared from the B-cells of various lymphoid tissues of 43 non-immunised donors using the "Quickprep mRNA Kit" (Pharmacia). First-strand cDNA was synthesized from mRNA using a "First-strand cDNA synthesis" kit (Pharmacia) using random hexamers to prime synthesis.

10 V-genes were amplified using family-specific primers for VH, VL and V κ genes as previously described (Marks et al., (1991) *J. Mol. Biol.* 222:581-597) and subsequently recombined together with the (Gly₄, Ser)₃ scFv linker by PCR assembly. The VH-linker-VL antibody constructs were cloned into the Sfi I and Not I sites of the phagemid vector, pCANTAB6. Ligation, electroporation and plating out of the cells was as described previously (Marks et al, *supra*). The library was made ca. 15000x larger than that described previously by bulking up the amounts of vector and insert used and by performing multiple 15 electroporations. This generated a scFv repertoire that was calculated to have ca. 1.3 x 10¹⁰ individual recombinants which by Bst NI fingerprinting were shown to be extremely diverse.

25 *2.2 Induction of phage antibody library to produce phage particles*

The phage antibody repertoire above was selected for antibodies which bind to adipocytes. The 'large' scFv repertoire was treated as follows in order to rescue phagemid 30 particles. 500ml prewarmed (37°C) 2YTAG (2YT media supplemented with 100 μ g/ml ampicillin and 2% glucose) in a 21 conical flask was inoculated with approximately 3x10¹⁰ cells from a glycerol stock (-70°C) culture of the library. The culture was grown at 37°C with good aeration until the OD_{600nm} 35 reached 0.7 (approximately 2 hours). M13K07 helper phage

(Stratagene) was added to the culture to a multiplicity of infection (moi) of approximately 10 (assuming that an OD_{600nm} of 1 is equivalent to 5×10^8 cells per ml of culture). The culture was incubated stationary at 37°C for 30 minutes 5 followed by 30 minutes with light aeration (200rpm) at the same temperature. The culture was centrifuged and the supernatant drained from the cell pellet. The cells were resuspended in 500ml 2YTAK (2YT media supplemented with 100µg/ml ampicillin and 50µg/ml kanamycin), and the culture 10 incubated overnight at 30°C with good aeration (300rpm). Phage particles were purified and concentrated by one polyethylene glycol (PEG) precipitation (Sambrook, J., Fritsch, E.F., & Maniatis, T. (1990). Molecular Cloning - A Laboratory Manual. Cold Spring Harbour, New York) and 15 resuspended in 9ml 10mM Tris containing 1mM EDTA (TE). 4.0g of CsCl was added to the phage stock and mixed gently to dissolve. A 11.5ml ultracentrifuge tube was filled with phage and centrifuged at 40 000rpm at 25°C for 24hr. The ultracentrifuge was stopped with the brake off and the clear 20 opalescent phage band collected using a pasteur pipette. Phage were dialysed at 4°C overnight against two changes of 1l of TE, titred and stored at 4°C.

2.3 Selection of phage from the large phage library which 25 bind to adipocytes

Selections were performed on either freshly isolated adipocytes or on plasma membrane fractions. In addition, the adipose tissue used in the selections was obtained from a number of different locations, i.e. subcutaneous, omental and 30 lipoma depots. By varying the types of selections performed and the adipose source we aimed to maximise the diversity of antibodies that were obtained and the range of antigens that they bind.

35 2.3.1 First round of selection

Freshly isolated adipocytes, but not plasma membrane fractions, were used for the first round of selection. This was to ensure that antibodies to the adipocyte cell surface only were selected at the first round, since selection on plasma membranes could yield antibodies binding only to intracellular antigens as well as those binding only to cell surface antigens. For each selection 50 μ l of isolated adipocytes were used, which is approximately 1x10⁵ cells.

These cells were prepared for selection by washing once in 250 μ l of Dulbeccos PBS plus 1% fatty acid free BSA. The washed adipocytes were then centrifuged for 1 minute at 1000rpm in a microfuge and the PBS removed from beneath the floating adipocytes.

Prior to selection, 1x10¹³ phage from the above library were preblocked in 250 μ l of 1% fatty acid free BSA, Dulbeccos PBS for 30 minutes at room temperature. The preblocked phage were then added directly to the freshly isolated adipocytes and incubated for 1 hour at 37°C with a single inversion every 15 minutes to mix. The adipocytes were then washed 3 times in Dulbeccos PBS plus 0.1% Tween 20 followed by 3 washes in Dulbeccos PBS. Each wash consisted of resuspending the cells in 250 μ l of wash buffer, followed by microfuging for 1 minute at 1000rpm and pipetting off the supernatant from beneath the adipocytes.

Elution of bound phage was achieved by mixing the adipocytes directly with 10ml of exponentially growing E coli TG1 with light aeration in 2TY broth at 37°C for 1 hour. Infected TG1's were plated on 2TYAG medium in 243mm x 243mm dishes. Dilutions of infected TG1s were also plated out and incubated at 30°C overnight. Colony counts gave the phage output titre.

2.3.2 Second round of selection

For the second round of selection, the round one outputs were

panned either on (1) freshly isolated adipocytes a second time, or (2) on an adipocyte plasma membrane preparation. Freshly isolated adipocytes were prepared for selections in the same way as described for round 1. The adipose tissue or 5 plasma membrane preparation used was also consistent with that used for round 1, i.e. if the adipose depot used at round one was subcutaneous then the same depot was used for round two. For selections on adipocyte plasma membranes, plasma membranes were coated onto immunotubes (Nunc) at 10 10mg/ml in 1ml of PBS overnight at 4°C. Uncoated material was washed away using PBS and the immunotube blocked with 1% fatty acid free BSA in PBS for 60 minutes at 37°C.

From the round one selections, colonies were scraped off the 15 243mm x 243mm plates into 3 ml of 2TY broth and 25% (v/v) glycerol added for storage at -70°C. Glycerol stock solutions from the first round of selection were rescued using helper phage to derive phagemid particles for the second round of selection. 250µl of a glycerol stock was used to inoculate 50 20 ml 2YTAK broth, and incubated in a 250 ml conical flask at 37°C with good aeration until the OD_{600nm} reached 0.7 (approximately 2 hours). M13K07 helper phage (moi=10) was added to the culture which was then incubated stationary at 37°C for 30 minutes followed by 30 minutes with light 25 aeration (200rpm) at the same temperature. The culture was centrifuged and the supernatant drained from the cell pellet. The cells were resuspended in 50ml prewarmed 2YTAK, and the culture incubated overnight at 30°C with good aeration. Phage particles were then obtained by centrifuging the overnight 30 culture at 13000rpm in a microfuge for 2 minutes. The supernatant, which contains approximately 1 x 10¹² phage per ml, was decanted into a fresh tube and the centrifugation repeated.

35 For the second round of selection using freshly isolated

adipocytes, 1ml of phage supernatant was concentrated by addition of 300 μ l 20%(w/v) PEG, 2.5M NaCl. The phage were precipitated for 1 hour on ice and recovered by microfuging for 10 minutes at 13000rpm. The supernatant was discarded and 5 the phage pellet resuspended in 250 μ l of Dulbecco's PBS containing 1% fatty acid free BSA. 1 μ l of this PEG precipitated phage, containing approximately 4×10^9 phage particles (assuming that an overnight rescue produces a phage titre of 1×10^{12} phage/ml), was diluted 1:400000 and 1 μ l (1×10^4 phage) 10 reinfected into *E.coli* to determine the actual input titre. The remaining preblocked phage (approximately 1×10^{12} phage particles) was then added directly to the cells and incubated for 1 hour at 37°C. As with round one, the adipocytes were inverted once every 15 minutes during this 15 binding step. The washing and elution steps were also identical to those described for round one.

For the selections on adipocyte plasma membranes, phage supernatants were preblocked in 1% fatty acid free BSA and 20 1xPBS for 30 minutes at room temperature. 1ml of preblocked phage was added directly to the plasma membrane coated immunotube and left stationary for 1 hour at 37°C. The tubes were then washed ten times with PBST and ten times with PBS. Phage were eluted by the addition of 100mM TEA for 10 minutes 25 at room temperature. The TEA was then neutralised with $\frac{1}{2}$ volume of 1M Tris.Cl, pH 7.6 and the eluted phage infected into exponentially growing TG1.

TG1 infection, plating out and titring was performed as 30 described for round 1.

2.3.3 Third round of selection

The outputs from the second round of selection were scraped off the large plates and phage rescued for a third round of 35 selection. The methods followed in the third round of

selection were identical to those described for round two. Briefly, selections were performed on either freshly isolated adipocytes or adipocyte plasma membranes and the choice of selection followed on directly from those performed at rounds 5 1 and 2. A summary of each type of selection performed (rounds 1 to 3) along with the output titres obtained is shown in Table 1.

2.4 Summary

10 The selection strategy was designed so that a large panel of anti-adipocyte antibodies binding several different antigens would be isolated from the large human scFv library. It was expected that the antibody-antigen interaction would be driven by the density of any given antigen on the adipocyte 15 cell surface. To maximise the diversity of antibodies produced, selections were performed using adipocytes from different depots, i.e. from either subcutaneous, omental or lipoma adipose tissue, as the nature of the antigens themselves or their cell surface density may vary between 20 depots. By selecting the antibody library on adipocytes from different adipose depots it was aimed to maximise the diversity of the clone panel obtained and to possibly isolate antibodies specific for each depot.

25 For each round of selection, freshly isolated adipocytes were used to ensure that antibodies subsequently isolated recognised antigens on the adipocyte cell surface. Generally the adipocytes were difficult to handle because (a) they float, and (b) they lyse if shaken too vigorously. Despite 30 these technical difficulties, the adipocytes were sufficiently stable to survive the selection and subsequent washing procedures. As an alternative approach, adipocyte plasma membranes were also used as part of the selection strategy as they are relatively easy to handle. However, to 35 avoid the isolation of antibodies to intracellular antigens,

selections were only performed on isolated adipocytes and not plasma membranes at round one. By avoiding the selection of antibodies to intracellular epitopes at round one (when the library has greatest diversity), only antibodies binding to 5 adipocyte cell surface antigens will be subsequently enriched at rounds 2 and 3. Therefore, plasma membranes were only used as an alternative to freshly isolated adipocytes in the second and third rounds of selection.

10 For each type of selection, three rounds of panning were performed. After each round of selection, ELISA analysis demonstrated that the number of clones binding to adipocyte plasma membranes increased from rounds one to three. This observation demonstrated that the number of antibodies that 15 recognised the adipocyte cell surface was being enriched with each round of selection even though the total output for each round did not vary a great deal. The anti-adipocyte antibodies isolated from these selections were then assessed by phage ELISA for adipocyte specificity (see Example 5).

20

EXAMPLE 3: SELECTION OF ANTIBODY-EXPRESSING PHAGE BY PANNING ON INTACT ADIPOSE TISSUE.

25 As well as panning the phage antibody library on freshly isolated adipocytes and plasma membranes, selections were also carried out on intact adipose. These selections used the same antibody repertoire as described in Example 2.

30 *3.1 Selections on intact adipose at different temperatures*
Selections on intact adipose tissue were performed as an alternative to using freshly isolated adipocytes. The disadvantage of taking this approach is that there is a range of cell types other than adipocytes present in adipose that will bind antibodies from the library, e.g. pre-adipocytes or 35 vascular endothelial cells. However, the principal benefit of

selecting on intact adipose is that collagenase will not have been employed. Collagenase (which contains trace amounts of other proteases) may potentially destroy some of the antigens of interest on the adipocyte cell surface during the 5 digestion step detailed in section 1.2.

In addition to selecting on intact adipose, the effect of varying temperature was also investigated. Selections are typically performed at 37°C, but at this temperature cell 10 surface receptors may be rapidly internalised (Walker F, J. Cell. Physiol., 130, 255, 1987). Therefore, selections were also performed at lower temperatures (4°C and room temperature) to minimize this effect.

15 Adipose tissue was prepared for selection by mincing into very small pieces (approximately 2-3mm thick) with scissors followed by washing in Dulbeccos PBS. One round of selection was then performed on these adipose tissue pieces as described in Example 2, with the exception that the 20 incubation temperatures used were 4°C and room temperature. Rounds two and three were performed only on adipocyte plasma membranes as described in Example 2, once again at 4°C and room temperature.

25 A summary of these selections and the output titres is given in Table 2.

3.2 Summary

Selections were performed on minced adipose tissue to isolate 30 antibodies to collagenase sensitive antigens/epitopes. By selecting the antibody library on intact tissue, antibodies would also be isolated to other antigens present in adipose, e.g. extracellular matrix antigens like collagen or antigens expressed by other cell types such as pre-adipocytes or 35 vascular endothelial cells. However, to prevent enrichment

of antibodies binding to antigens on cell types other than adipocytes, rounds 2 and 3 were performed on adipocyte plasma membranes to select for adipocyte binding clones only.

5 The output titres for selections at both 4°C and 25°C shared similar trends. High output titres were observed after the first round of selection, at least 10-100 fold above those seen for the selections on isolated adipocytes (see Example 2). These higher titres most likely reflect that intact 10 tissue has been used for selections rather than a single cell type such as an adipocyte. These antibodies were then assessed by phage ELISA for adipocyte specificity (see Example 5).

15 *EXAMPLE 4: PROXIMOL SELECTION OF ANTIBODY-EXPRESSING PHAGE USING AN ANTI-ADIPOCYTE POLYCLONAL SERUM AS THE TARGETING REAGENT*

20 *4.1 ProxiMol Selections using an anti-adipocyte polyclonal serum*

It is possible to target phage antibody libraries to cell surface proteins by using targeting molecules such as their natural ligands or specific antibodies to the proteins of 25 interest (monoclonal or polyclonal). Here, a rabbit polyclonal anti-adipocyte serum was employed to guide phage antibodies to proteins on the adipocyte cell surface using the method described by Osbourn et al (Immunotechnology, 3, 293, 1998, and WO98/01757).

30 *4.2 Generation and Characterisation of the Rabbit Anti-Adipocyte Polyclonal Serum*

To generate antibodies against human adipocyte plasma membranes, rabbits were immunised 4 times with 100µg human 35 adipocyte plasma membranes at 28 day intervals and serum

samples taken. The serum was characterised by ELISA and shown to bind human adipocyte plasma membranes at dilutions down to 1:100000. However, the serum is not specific for adipocytes and cross-reaction was observed to plasma membrane 5 preparations from other cell lines, e.g. Chang liver hepatocytes, lung fibroblast cell line CCD-19Lu, macrophage like cell line U937 and human umbilical cord endothelial cell line HuVEC. However, this cross-reaction is not observed at serum concentrations below 1:1000, so the serum is relatively 10 specific for adipocyte antigens.

4.3 ProxiMol selection using the anti-adipocyte rabbit polyclonal serum as a targetting agent

The antibody library described in example 2 was also used in 15 these selections. To prepare the rabbit polyclonal serum for ProxiMol, it was first necessary to conjugate it to HRP using an HRP conjugation kit (Pierce 31494). ELISA was employed to determine that the HRP conjugation was successful and to empirically determine the optimal HRP-polyclonal 20 concentration to use in ProxiMol. Adipocyte plasma membranes (10 μ g/ml in PBS) were coated overnight at 4°C onto 96 well polystyrene plates (Falcon 3912). Uncoated material was washed away using PBS and each well blocked with 200ml of 3% Marvel in PBS for 1 hour at 37°C. A serial dilution (1:10, 25 1:100 and 1:1000) of the HRP conjugated anti-adipocyte serum in 3% Marvel/PBS was then applied to the plasma membrane coated wells of a 96 well plate and incubated for 1hour at 37°C. Unbound antibody was washed away with 3 PBST washes followed by 3 PBS washes. Bound antibody was then detected 30 with TMB substrate (Sigma T-8665). Colour was allowed to develop to a suitable intensity, the reaction was then stopped by the addition of $\frac{1}{2}$ volume 0.5M H₂SO₄ and the absorbance of each well measured at 450nm. In this ELISA the polyclonal-HRP conjugate was shown to bind effectively to 35 adipocyte but not hepatocyte plasma membranes at a dilution

of 1:100.

The first round of ProxiMol selection was conducted as described in Example 2, i.e adipocytes were freshly prepared and incubated together with the large scFv library. However, for a ProxiMol selection, the anti-human adipocyte polyclonal conjugated to HRP was simultaneously added to a final concentration of 1:100. Parallel selections were set up, one incubated at 4°C and the other at room temperature (25°C).

For both selections, the incubation time was two hours and the tubes were inverted once every 20 minutes to ensure mixing. The adipocytes were then washed 3x with PBST and 3x with PBS. The selections were then treated with biotin tyramine. In the presence of HRP and hydrogen peroxide biotin tyramine becomes free radicalised and is deposited around the site of HRP activity. Because the half life of the free radical is very short, deposition is highly localised around the site of enzyme activity and only phage which bind close to the site of the original HRP binding site and hence the target antigen, become biotinylated. These phage can be specifically recovered from the background population of non-biotinylated phage.

Biotin tyramine treatment consisted of incubating the selections for 10 min at room temperature with 250µl of biotin tyramine mix containing 0.03% hydrogen peroxide in 50mM Tris-HCl pH 7.4 with a 1:600 dilution of biotin tyramine. Biotin tyramine was prepared by the addition of 5mg of NHS-LC-biotin to 1.55mg tyramine in 2ml 50mM borate, pH 8.8 followed by turning end over end at room temperature in the dark, then filtering through a 45mm filter. The biotin tyramine was aliquotted and stored at -70°C. After the 10 min incubation with biotin tyramine mix the adipocytes were washed in PBST and PBS as before and 500µl of 100mM TEA added to elute bound phage. Incubation was for 10 min at room

temperature, after which the adipocytes were centrifuged for 1 minute at 1000rpm and the eluted phage transferred from beneath the adipocyte layer into a fresh tube containing 250 μ l of 1M Tris pH7.4.

5

Eluted phage were added to 50 μ l of streptavidin coated Dynal beads which had been pre-blocked in PBS containing 3% Marvel (3%MPBS). Phage were incubated with the beads for 15 min at room temperature with end over end rotation in the presence of 3%MPBS. Beads were then washed three times in 1ml of PBST, transferred to a fresh eppendorf and washed three times in 1ml PBS. Finally the beads were resuspended in 100 μ l of PBS and 50 μ l of this used to infect TG1 *E.coli* as described in Example 2.

15

Phage from the first round of selection were rescued as described in Example 2, and a second round of ProxiMol selection carried out exactly as the first, except that both freshly isolated adipocytes and adipocyte plasma membranes were used. The temperature of the second round of selection remained consistent with the first, i.e. a 4°C incubation at round 1 was followed by another 4°C incubation at round 2.

25 A summary of the ProxiMol selections and the output titres is given in Table 3.

4.4 Summary

The majority of selections have involved panning on either freshly isolated adipocytes, intact adipose tissue or 30 adipocyte plasma membranes. By panning the antibody library on whole cells in this way the inventors expected the selection outputs to be largely driven by antigen density, i.e. the inventors expected antibodies binding to the more abundant antigens on the adipocyte cell surface and fewer 35 antibodies binding to less abundant antigens.

With the aim of deriving a panel of antibodies with different specificities to those obtained by direct panning, ProxiMol selections were also performed, these allowing for the antibody library to be selected in a more targeted manner 5 using, for example, natural ligands or antibodies. In this instance, the inventors opted to use a rabbit polyclonal antiserum that had been raised against human adipocyte plasma membranes. The antibodies in this serum were used to guide the phage antibody library to antigens on the adipocyte cell 10 surface that were originally immunogenic in the rabbit.

The ProxiMol selections were performed at either 4°C or 25°C to avoid possible receptor internalisation and the outputs observed were lower than those seen for direct panning. This 15 is as expected since a more targeted approach yields fewer antibodies than would selections on an entire cell surface. The antibodies from these selections were then assessed by phage ELISA for adipocyte specificity (see Example 5).

20 *EXAMPLE 5: IDENTIFICATION & CHARACTERISATION OF SELECTED
ANTIBODIES BY ADIPOCYTE PLASMA MEMBRANE ELISA AND DNA
SEQUENCING*

5.1 *Adipocyte plasma membrane ELISA*

25 With the aim of identifying clones from the selections that bind to adipocyte cell surface antigens, phage antibodies were initially screened by ELISA against both adipocyte and Chang liver hepatocyte plasma membranes. This ELISA would allow us to identify antibodies that recognise the adipocyte 30 cell surface and simultaneously eliminate those antibodies binding common house-keeping proteins present on other cell types.

35 Phage ELISAs were carried out as follows: individual colonies were picked into a 96 well tissue culture plate containing

100 μ l 2YTAK. Plates were incubated at 37°C for 6 hours. M13KO7 helper phage was added to each well to an moi of 10 and incubated for 30 min at 37°C followed by gentle shaking for 30min at 37°C. The plates were centrifuged at 2000 rpm for 10min and the supernatant removed. Cell pellets were resuspended in 100 μ l 2TYAK and incubated at 30°C overnight. Each plate was centrifuged at 2000 rpm and the 100 μ l phage-containing supernatant from each well recovered and 20 μ l of 6x PBS containing 18% Marvel™ blocking solution added and then incubated at room temperature for 1 hour. Meanwhile, 10 Falcon™ 96 well polystyrene plates, coated overnight with adipocyte and hepatocyte plasma membranes at 10 μ g/ml in PBS, were blocked for 2 h at room temperature in PBS containing 3% Marvel (3MPBS). These plates were then washed three times 15 with PBS and 50 μ l preblocked phage added to each well. The plates were incubated stationary at room temperature for 1 h after which the phage were flicked out. The plates were washed with three changes of PBST followed by three changes of PBS at room temperature.

20 To each ELISA plate well, 50 μ l of a 1 in 5000 dilution of the anti-gene8-HRP conjugate (Pharmacia) in 3MPBS was added and the plates incubated at room temperature for 1 h. Each plate was washed with 3xPBST followed by 3xPBS. 50 μ l of TMB 25 substrate was then added to each well, and incubated at room temperature for approximately 30 minutes, after which the colour reaction was stopped by the addition of 25 μ l of 0.5M H₂SO₄. The absorbance signal generated by each clone was assessed by measuring the optical density at 450nm using a 30 microtitre plate reader. Clones were chosen for further analysis if an ELISA signal was observed on adipocyte but not hepatocyte plasma membranes. Of 4400 clones screened from the above selections, over 800 were scored positive by this adipocyte phage ELISA that did not recognise the liver 35 hepatocyte cell line plasma membranes. Thus, over 800 phage

antibodies were identified to antigens present on adipocytes that are not on liver hepatocytes.

5.2 DNA Sequencing of anti-adipocyte antibodies

5 The nucleotide sequences of the adipocyte binding antibodies were determined by first using vector-specific primers to amplify the inserted DNA from each clone. Cells from an individual colony on a 2YTAG agar plate were used as the template for a PCR amplification of the inserted DNA using
10 the primers pUC19reverse and fdtetseq (Osbourne et al, J. Immunotechnology, 2, 181-96, 1996). Amplification conditions consisted of 30 cycles of 94°C for 1 min, 55°C for 1 min and 72°C for 2min, followed by 10 min at 72°C. The PCR products were purified using a PCR Clean-up Kit (Promega) in to a
15 final volume of 50µl H₂O. 5 µl of each insert preparation was used as the template for sequencing using the Taq Dye-terminator cycle sequencing system (Applied Biosystems). The primers pUC19reverse and fdtseq were used to sequence the heavy and light chain of each clone respectively.

20 The VH and VL segments of the anti-adipocyte clones were then DNA sequenced. From this data we were able to identify 200 unique antibodies for further analysis.

25 5.3 Specificity ELISA

In order to focus on antibodies potentially binding to novel adipocyte cell surface proteins, a more extensive screen was then performed with the aim of identifying and excluding anti-adipocyte antibodies that were recognising common cell
30 surface or house-keeping proteins expressed by a number of different cell types. The 200 unique antibodies were analysed by phage ELISA for binding to adipocyte plasma membranes but not to plasma membranes from one or more of liver hepatocytes (Chang), erythrocytes, lung fibroblasts (CCD-19Lu),
35 macrophage like cells (U937) and human umbilical cord

endothelial cells (HuVEC).

Individual clones were picked into 50ml Falcon tubes containing 5ml 2YTAG. The tubes were incubated at 37°C for 6 hours. M13KO7 helper phage was added to each tube to an moi of 10 and incubated for 30 min at 37°C followed by gentle shaking for 30min at 37°C. The tubes were centrifuged at 3000 rpm for 10min and the supernatant removed. Cell pellets were resuspended in 5ml 2TYA with kanamycin (50µg/ml) and incubated at 30°C overnight. Each tube was centrifuged at 3000 rpm and 100µl of phage-containing supernatant recovered and blocked with the addition of 20µl 6x PBS containing 18% Marvel™ at room temperature for 1 hour. The phage ELISAs were then performed as described above, with all the plasma membrane preparations being coated overnight at 10µg/ml.

From this additional specificity ELISA, 108 clones were identified that bound to adipocyte but not to hepatocyte, erythrocyte, lung fibroblast, Huvec or U937 plasma membranes. Each of these antibodies is unique as determined by DNA sequencing (see 5.2 above). The sequences are provided below. Note that a number of the antibodies share light chains in common: the sequences for these are not duplicated but are cross-referenced to each other. Table 5 shows the SEQ ID NO.'s for the VH and VL domains. The individual VH and VL segments of the antibodies were aligned to the germline sequences in V-base (Tomlinson et al, MRC centre for Protein Engineering, <http://www.mrc-cpe.cam.ac.uk>) and the closest germline identified. The result of the V-base search is shown in Table 4, together with the VH CDR3 sequence as a further indication of antibody diversity.

5.4 Adipocyte depot ELISA

As described in Examples 2-4, selections were performed on adipocytes isolated from different body depots. To determine

if any of the antibodies isolated were specific for a particular type of adipose tissue, an ELISA was performed using adipocyte plasma membranes isolated from different depots, i.e. abdominal fat, breast fat, back fat, omental 5 (intra-abdominal) fat and lipoma fat.

All the clones tested in this ELISA were shown to bind to adipocyte plasma membranes from each of the adipose depots. For example, see Figure 1 for results obtained for Fat 37.

10 As shown in Figure 1, in ELISA Fat 37 is seen to bind adipocyte plasma membranes from each of the fat depots investigated.

15 *5.5 Summary*

From the selections (see Examples 2 to 4), a total of 4400 clones were initially screened for specificity by ELISA on both adipocyte and hepatocyte plasma membranes. This preliminary ELISA identified 800 anti-adipocyte antibodies 20 that did not cross-react with liver hepatocytes. These clones were then DNA sequenced and 200 unique anti-adipocyte antibodies identified.

These 200 clones were then screened extensively by ELISA to 25 eliminate those clones binding to one or more of a number of cell types: liver hepatocytes (Chang), erythrocytes, lung fibroblasts (CCD-19Lu), macrophage like cells (U937) and human umbilical cord endothelial cells (HuVEC). The aim of this screen was to identify those clones with the highest 30 specificity for adipocytes and eliminate those that are binding to common house-keeping proteins expressed by a number of cell types. Of the selections described in Examples 2 to 4, those performed using intact adipose tissue generated the highest proportion of antibodies showing cross-reaction 35 with other cell types. In contrast, relatively few

cross-reactive clones were identified in either the adipocyte panning selections or the ProxiMol™ selection. Taken together, these results demonstrate that the likelihood of isolating an antibody with high specificity for a given cell type is increased if that cell is first isolated away from surrounding cell types present in the tissue. Of the 200 clones screened in this specificity ELISA, 108 were identified as adipocyte specific. Each of these antibodies was then further characterised by ICC on normal human tissues (Example 6).

EXAMPLE 6: CHARACTERISATION OF ANTI-ADIPOCYTE ANTIBODIES BY IMMUNOCYTOCHEMISTRY ON HUMAN TISSUES

15 The clones identified as adipocyte reactive in ELISA (Example 5) were then analysed further by ICC.

In the first instance all antibodies were screened on a tissue rich in adipocytes, such as breast, to confirm that 20 each antibody recognised native adipocytes *in situ*.

Antibodies which bound adipose tissue sections were then screened on all (or a subset) of the following panel of normal human tissues: adrenal gland, aorta, bladder, blood vessels, bone marrow, breast, cerebrum, cerebellum, cervix, 25 colon, duodenum, endometrium, fallopian tube, heart, ileum, kidney, liver, lung, lymph node, nerve, oesophagus, ovary, pancreas, parathyroid gland, parotid gland, pituitary gland, placenta, prostate gland, skin, spinal cord, spleen, stomach body, skeletal muscle, testis, thyroid gland, tonsil and 30 ureter.

6.1 Preparation of tissues for ICC

Human tissues were obtained mostly from post-mortem samples. Tissues were cut into 5mm³ chunks and mounted onto cork pieces 35 using a drop of OCT compound (Tissue-Tek, Miles Inc, Elkhart,

USA). To freeze the tissues, 20 mls of isopentane was cooled in a bath of liquid nitrogen and the mounted tissues immersed for 30 seconds. The frozen tissues were then placed into a cryotube and immersed in liquid nitrogen for a further 30
5 seconds. Tissue blocks were stored frozen at -70°C.

To cut sections, OCT compound was applied to a cryostat chuck and the frozen tissue embedded. The chuck and tissue were then snap frozen for 30 seconds in liquid nitrogen. The
10 tissue was then mounted onto a cryostat and 5 micron cryosections of each human tissue cut onto microscope slides.

6.2 Preparation of phage antibodies for ICC

Phage antibody clones were inoculated into 5ml 2TYAG in 50ml
15 Falcon tubes and grown at 37°C with aeration for 5 hours. M13K07 helper phage was added to each tube at an moi of 10 and incubated stationary for 30 min at 37°C followed by gentle shaking for 30 min at the same temperature. The tubes were centrifuged at 3000 rpm for 10 min and the supernatant
20 removed. Cell pellets were resuspended in 5ml 2TYKA and incubated at 30°C overnight. Tubes were centrifuged at 3000 rpm for 10 min and the phage antibody supernatant collected from each tube and preblocked with 1% BSA before use in ICC.

25 6.3 ICC on sections of normal human tissue

Human tissue sections were fixed by immersion in acetone at ambient temperature for 10 min, air dried and then washed once for 10 min in PBS. Sections were blocked in 5 µg/ml streptavidin in PBS for 15 min, washed 3 times in PBS and
30 incubated in 10 µg/ml biotin in PBS for 15 min. Sections were washed 3 times in PBS and then incubated for 30 min in PBS containing 1% BSA (fatty acid free). Phage antibody supernatants preblocked in 1% BSA were incubated on the sections for 2 hr at ambient temperature. Slides were washed
35 3 times in PBST and incubated with an anti-M13-HRP conjugate

(Pharmacia) diluted 1/500 in PBS containing BSA. Sections were washed 3 times in PBST and a biotin tyramine amplification step then carried out. Biotin tyramine amplification consisted of incubation of the section with 5 biotin tyramine diluted 1/600 in 50mM Tris-HCl, pH 7.4 containing 0.03% hydrogen peroxide for 10 min at room temperature, after which the slides was washed in 3 times in PBST. Sections were then incubated for 30 min in streptavidin-HRP complex (DAKO K0377) diluted in PBS, and 10 then washed 3 times in PBST and once in PBS. Sections were stained by incubation with 3-amino-9-ethyl-carbazole (AEC, Sigma). AEC substrate was prepared by diluting a stock solution (2.4 mg/ml of AEC dissolved in dimethylformamide) 1:10 in 20mM sodium acetate buffer, pH 5.2 and adding 0.15% 15 (v/v) of H₂O₂. 100ml of substrate solution was then pipetted onto each section and incubated for 5-10 min followed by washing in water to stop colour development. The slides were then counterstained with haemotoxylin (DAKO) for <5 seconds and then washed 3 times in water. Washed sections were then 20 coated in aqueous mount and a glass cover slip applied.

6.3.1 Adipocyte Staining

108 antibodies, which had been isolated by virtue of their binding to adipocyte plasma membranes in ELISA, were first 25 screened by phage antibody ICC on adipose tissue sections. 85 of the antibodies stained adipocytes on adipose tissue sections whereas 26 did not. This is either a consequence of the insensitivity of the ICC technique relative to ELISA, or that the antibodies recognise an epitope exposed on adipocyte 30 plasma membranes but not on native adipocytes. All the clones that recognised adipocytes in adipose sections were subsequently shown to stain adipocytes in any tissue that contains adipocytes, for example, breast, skeletal muscle, skin, peripheral nerve, heart, thyroid gland, adrenal gland 35 and parotid gland. This was also true in ELISA using

different adipocyte plasma membrane preparations (see 5.4).

Qualitatively, therefore, all the 85 different antibodies appear to recognise all fat depots. Quantitatively, adipocyte 5 membrane staining fell into 3 categories:

- 1) strong uniform staining
- 2) "weak patchy" - characterised by antibody binding to the cytoplasm surrounding the adipocyte nucleus (which is 10 flattened to the side of the cell),
- 3) "dotted patchy" - characterised by an incomplete but regular staining of the membrane

This variation in adipocyte staining pattern is most likely 15 due to the density of the target antigen and/or to a lesser extent the affinity of each antibody for its antigen.

6.3.2 Cross-reactivity with Human Tissues

In addition to adipocyte staining, all antibodies also 20 recognised at least one other cell type present in one or more human tissues.

6.3.2.1 Common cross-reactivity:

ICC patterns emerged whereby certain tissues were frequently 25 recognised by many of the anti-adipocyte antibodies. The 9 tissues, apart from adipose, most frequently bound were spleen, heart, kidney, colon, liver, skin, striated muscle, tonsil and testis (see Table 6).

30 A description of the cell types and structures recognised by the anti-adipocyte antibodies in these tissues is summarised below, each exemplified by one or more antibodies:

(a) Spleen

35 red pulp of spleen, primarily to the sinusoidal network

(b) Heart and Striated muscle

capillaries that line either the cardiac or striated muscle fibres, walls of larger blood vessels

(c) Kidney

5 capillaries, larger blood vessels, general punctate staining throughout the kidney, kidney tubules and glomeruli

(d) Colon

10 capillaries, larger blood vessels, smooth muscle in the muscularis externa

(e) Liver

general punctate staining of hepatocytes, liver sinusoids

(f) Skin

15 capillaries, larger blood vessels, smooth muscle, sebaceous glands

(g) Tonsil:

20 post-capillary venules, blood vessels in the germinal centres, general punctate staining throughout the tonsil, lymphocytes

(h) Testis

capillaries, larger blood vessels, seminiferous tubules

6.3.2.2 Infrequent cross-reactivity

25 For a smaller proportion of the antibodies, binding to tissues other than those described in 6.3.2.1 was observed. The tissues and cell types recognised are described below and exemplified by one or more antibody:

(a) Breast - mammary lobules (Fat 2, Fat 7, Fat 19 and Fat 30 20)

(b) Thyroid gland - large blood vessels (Fat 1, Fat 26, Fat 36, Fat 40 and Fat 97)

(c) Peripheral nerve - epineurium tissue (Fat 31)

(d) Cerebellum - granular layer (Fat 17)

35 - molecular layer (Fat 29)

- connective tissue (Fat 117)
- (e) Endometrium - epithelial cells (Fat 36)
- (f) Myometrium - blood vessels (Fat 115)
- (g) Lung - connective tissue and large blood vessels (Fat 40)

5

6.3.2.3 Extensive ICC Screen

A number of the antibodies have been extensively screened on a large panel of normal human tissues. These screens allow us to build a complete tissue binding profile for individual 10 antibodies. For example, the antibody Fat 13 has been screened on 37 normal male and female tissues: adrenal gland, aorta, bladder, blood vessels, bone marrow, breast, cerebrum, cerebellum, cervix, colon, duodenum, endometrium, fallopian tube, heart, ileum, kidney, liver, lung, lymph node, nerve, 15 oesophagus, ovary, pancreas, parathyroid gland, parotid gland, pituitary gland, placenta, prostate gland, skin, spinal cord, spleen, stomach body, skeletal muscle, testis, thyroid gland, tonsil and ureter. Fat 13 binding was restricted to adipocytes and to capillary endothelial cells 20 in the following tissues:

- (a) Adipocytes in breast, colon, skin, heart, striated muscle, nerve, parotid gland, adrenal gland and parathyroid gland
- (b) Capillary endothelial cells in heart, colon, striated 25 muscle, breast, cerebellum skin and liver (sinusoids).

Thus, the phage antibody Fat 13 recognises an epitope/antigen that is present on the adipocyte cell surface that is shared only with capillary endothelial cells. This antibody 30 therefore shows a remarkable specificity and identifies an antigenic link between adipocyte and vasculature biology.

6.4 Summary

A method has been successfully developed to allow analysis of 35 phage antibodies by ICC. Of 108 anti-adipocyte antibodies

identified by ELISA, 85 were shown to bind to native adipocytes in situ. These 85 clones have been screened by ICC on a panel of normal human tissues.

5 All the antibodies showed cross-reaction with one or more of the tissues screened. This cross-reaction was often limited to only a few cells in a particular tissue, for example to capillary endothelial cells in colon. As the antibodies were all 'adipocyte specific' in ELISA (see Example 5), the
10 ability of ICC to visualise antibody binding to relatively minor tissue components demonstrates its use as a tool in the assessment of antibody binding profiles.

One feature of the ICC profiles of the anti-adipocyte
15 antibodies was the cross-reaction observed in a number of common tissues. The most frequently bound tissues were spleen, heart and colon and to a lesser extent skeletal muscle and kidney. Other than adipocytes, the most commonly bound cells/structures observed in these tissues were
20 capillary endothelial cells and the smooth muscle walls of large blood vessels.

The ICC profiles raise interesting implications for the relationship between adipocytes and other cell types. For
25 example, it is well established that adipocytes and muscle cells both differentiate from the same precursor, or stem cell. That some of the antibodies described here bind to both adipocytes and smooth muscle suggests that the two cell types continue to express common antigens post-differentiation of
30 the stem cell. Thus the antibody panel may be used to study development and biology of the precursor cell through to the mature adipocyte.

Moreover, the common staining patterns that were observed
35 provide indication that there are antigens which are shared

by adipocytes and other cell types and that these in turn reflect a common biology or pathology. For example, the binding of some antibodies (e.g. Fat 13) to adipocytes and blood vessels indicates a common antigen in these two 5 tissues. This antigen may therefore be involved in both adipocyte and blood vessel biology and pathological states where the two cell types are involved, for example in atherosclerosis. Alternatively, the cardiovascular staining pattern link between adipocytes and heart tissue may be 10 connected to the high incidence of heart disease in obese individuals. Hence, the antibody panel is useful in further characterisation of the antigens on the adipocyte cell surface, their biology and the link with a variety of pathological conditions.

15

EXAMPLE 7: CHARACTERISATION OF ANTIGENS RECOGNISED BY THE ANTI-ADIPOCYTE ANTIBODIES

The panel of anti-adipocyte antibodies were isolated by (a) panning on either the adipocyte cell surface or on intact 20 adipose tissue, or by (b) ProxiMol using a rabbit polyclonal antiserum that had been raised against human adipocyte plasma membranes. As a consequence of these selections, an extensive panel of antibodies that bind to the cell surface of adipocytes has been generated and these may be used to 25 recognise a variety of different epitopes/proteins which may be important to adipocyte biology.

Experiments were performed to characterise the antigens bound by some of these anti-adipocyte antibodies, allowing for 30 their identification.

7.1 Characterisation of Antigens using Protein Chemistry

Four antibodies were investigated in the first instance: Fat 13, Fat 37, Fat 40 and Fat 41. Of these antibodies, Fat 13, 35 Fat 37 and 41 were screened as rat chimeric IgG molecules (i.e.

IgG composed of rat constant domains coupled to human variable domains) whereas Fat 40 was screened as a scFv which had been purified by IMAC. All antibodies bound to adipocyte plasma membranes in ELISA and did not cross-react with the 5 other cell types tested (see example 5 for details). In ICC, all clones strongly stained adipocytes in the human tissues screened. In addition, Fat 13, 37 and 41 all bound to capillaries in a number of tissues (particularly in heart). However these antibodies had different ICC tissue profiles, 10 for example Fat 13 staining was restricted to adipocytes and capillaries whereas Fat 37 was also shown to bind the basal lamina in kidney. The ICC profile of Fat 40 was characterised by adipocyte and smooth muscle staining in many tissues.

15 7.2 SDS-PAGE western blotting

7.2.1 Method

Adipocyte plasma membranes, prepared as described in example 1, were boiled in SDS-PAGE sample buffer for 5 minutes at 20 90°C (2x SDS-PAGE sample buffer: 0.5M Tris-HCl pH6.8, 20% (v/v) glycerol, 10% (w/v) SDS, 20mM DTT, 0.1% (w/v) bromophenol blue). The membranes were then loaded, approximately 10µg per lane, onto 14% polyacrylamide gels supplied by Novex (Cat no. EC64855), in addition to a full 25 range (250 to 10 kDa) of molecular weight marker. Samples were electrophoresed in SDS-PAGE running buffer (25mM Tris, 192mM glycine, 0.1% (w/v) SDS) for 2-3 hours at 100V and maximum current. Electrophoresis was stopped when the bromophenol blue dye front had reached the bottom of the gel. 30 Proteins were then transferred from the gel to PVDF membrane. Blotting cassettes were prepared by soaking the following in transfer buffer (12mM Tris, 96mM Glycine, 20% (v/v) methanol) and then assembling in order:
(a) Three scotchbrite pads
35 (b) One piece of 30mm thick blotting paper

- (c) Gel
- (d) PVDF membrane
- (e) One piece of 30mm thick blotting paper
- (f) Three scotchbrite pads

5

The assembled cassette was inserted into the Novex blotting tank and immersed in transfer buffer, with the PVDF nearest the anode. Transfer of proteins from gel to PVDF was achieved overnight at 10 volts, maximum current and 4°C. PVDF membranes were then removed to a separate dish and incubated in 3% Marvel in PBS (Blotto) for 1 hour with shaking. The membranes were washed twice in PBS and then incubated with the primary antibodies at 10µg/ml in Blotto for 1 hour.

10 15 For scFv western blots, the PVDF membrane was washed three times in PBST and then incubated with the anti-myc antibody 9E10 diluted 1:100 in Blotto for 1 hour. After a further three washes in PBST, scFv westerns were then incubated with an anti-mouse IgG HRP conjugate antibody (Sigma) diluted 20 1:1000 in Blotto for 1 hour.

25 Rat IgG westerns were washed three times in PBST and then incubated with an anti-rat Ig Kappa light chain HRP conjugate antibody (Pharmingen) diluted 1:3000 in Blotto for 1 hour.

30 For both systems, blots were extensively washed in PBST (3 washes of 15 minutes) and then once in PBS for 15 minutes. Blots were then developed using the ECL detection system (Amersham). The blots were incubated with the substrate luminol which emits light when oxidised by HRP. This light emittance was then detected on photosensitive film.

7.2.2 Result of SDS-PAGE Western Blotting

35 Of the antibodies screened on adipocyte plasma membranes, only fat 37 has been shown to bind to its target antigen, a

protein of approximately 35KDa. The lack of binding seen for the other clones tested suggests that they recognise conformationally dependant epitopes. All proteins are denatured under SDS-PAGE conditions and it is unlikely that 5 conformational epitopes would remain intact, resulting in an apparent loss of antibody reactivity.

7.3 Native-PAGE western blotting

10 7.3.1 Method

To avoid denaturation of target antigens, adipocyte plasma membranes were electrophoresed under near native conditions. As most membrane proteins require the presence of detergents to maintain solubility in aqueous solution, the SDS was 15 replaced with a milder ionic detergent, deoxycholic acid. This detergent is similar to SDS in that it also carries an overall negative charge, thus all dissolved proteins will migrate toward the anode during electrophoresis. To confirm that this detergent is non-denaturing, all the antibodies 20 were screened by ELISA against adipocyte plasma membranes solubilised in deoxycholic acid. No loss of binding was observed for any antibody (Fat 13, 37, 41 or 10C12).

Therefore, in this procedure adipocyte plasma membranes were 25 not boiled but were loaded directly onto 4% Novex gels (Cat no. EC60555) in native loading buffer (2x: 0.5M Tris-HCl pH 8.8, 20% (v/v) glycerol, 0.1% (w/v) bromophenol blue). Samples were electrophoresed in native running buffer (25 mM Tris, 192 mM glycine, 2 mM deoxycholic acid) for 2-3 hours at 30 100V and maximum current. Electrophoresis was stopped when the bromophenol blue dye front had reached the bottom of the gel. The proteins were then transferred from the gel to PVDF membrane in native transfer buffer (12 mM Tris, 96 mM Glycine, 0.2 mM deoxycholic acid). The remainder of the 35 blotting procedure followed that described in 7.2.1.

7.3.2 Result of Native Western Blotting

On native Western blots, all of the antibodies except Fat 13 were demonstrated to bind to their target antigen. However, the molecular weights of the antigens cannot be deduced from 5 these native gels, as proteins do not separate according to size but to overall net charge. Under these conditions it was apparent that Fat 41 was binding to a protein with the same overall net charge as Fat 37. Coupled with the SDS-PAGE data, this result suggests that these two antibodies are binding to 10 different epitopes of the same 35 kDa protein. Fat 40 also bound to a protein but to one with a different net charge to that bound by Fat 37 and Fat 41 - a result which suggests that Fat 40 is binding to a different antigen. The lack of binding seen for Fat 13 could be a consequence of antibody 15 binding to a conformational epitope which is also sensitive to deoxycholic acid as well as SDS. Both detergents are ionic but deoxycholic acid is considerably milder and would result in less disruption to the overall conformation of the protein. This enabled the antigens for Fat 40 and 41 to be 20 recognised but for Fat 13 an alternative detergent to deoxycholic acid, e.g. Triton, would have to be considered for further western blots.

7.4 Effect of temperature on Antigen Stability

7.4.1 Method

This study was performed as a follow up to the Western blots to gain further information on the stability of the antigens recognised by the antibodies. Adipocyte plasma membranes, 25 diluted to 10 μ g/ml in PBS, were heated in 5°C increments from 50°C to 75°C for 20 minutes. The heated plasma membranes were then cooled to room temperature and coated directly onto Falcon 96 well polystyrene plates overnight at 4°C.

An ELISA was then performed with each antibody, i.e. Fat 13, 35 Fat 37 & Fat 41 rat chimeric IgG each at 1 μ g/ml and Fat 40

scFv at 10mg/ml. Initially, the 96 well plates were washed once with PBS and 200 μ l of 3% Marvel in PBS (Blotto) added to each well for 1 hour at 37°C. The plates were washed twice in PBS and then incubated with the primary antibodies diluted in 5 Blotto for 1 hour at 37°C.

For a scFv ELISA, plates were washed three times in PBST followed by three washes in PBS and then incubated with the anti-myc antibody 9E10 diluted 1:250 in Blotto for 1 hour at 10 37°C.

Rat IgG ELISAs were washed three times in PBST followed by three washes in PBS and then incubated with an anti-rat IgG_{2b} antibody (Pharmingen) diluted 1:1000 in Blotto for 1 hour at 15 37°C.

For both systems, a further three washes in PBST and PBS were performed and the plates probed with an anti-mouse IgG HRP conjugate antibody (Sigma) diluted 1:1000 in Blotto for 1 20 hour at 37°C. The plates were washed three times in PBST followed by three washes in PBS and then developed using TMB substrate until a sufficient level of colour had developed. Developing was stopped by the addition of $\frac{1}{2}$ volume of 0.5M H₂SO₄ and the absorbances measured at 450 nm.

25

7.4.2 Result of Antigen Stability Experiment

From Figure 2 it can be seen that Fat 37 and Fat 41 follow similar profiles, i.e. their epitopes are not affected by heating to 55°C but are both denatured at 65°C. This result 30 supports the observations seen on the Western blots in that the two antibodies appear to be binding to the same antigen. Fat 13 also shows a similar profile to that seen for Fat 37 and Fat 41. However, Fat 40 gives a distinctly different profile to the other antibodies suggesting, again, that it is 35 binding to a different antigen.

7.5 Determination of *pI* using *Rotofor*

The Rotorfor system (Biorad) fractionates complex protein samples in free solution using preparative IEF. The system uses ampholytes to generate linear pH gradients which are then used to fractionate proteins on the basis of their *pI* (isoelectric point).

This Rotorfor system was used to fractionate proteins from an adipocyte plasma membrane preparation. In total, 1mg of human

10 adipocyte plasma membranes solubilised in 0.1% (v/v) Triton X-100 were applied to the Rotorfor cell. These were mixed with an ampholyte buffer ranging from pH 3 to pH 10 and focussed overnight (10W, 3000V max and 150mA max). Using a vacuum assisted system, the fractions were harvested by

15 simultaneous aspiration into 20 separate tubes. As the Rotorfor system is non-denaturing the resolved proteins can be coated directly onto 96 well polystyrene plates for ELISA analysis, avoiding the need to perform any western blotting.

20 A 1:2 dilution of each of these fractions was coated onto Falcon 96 well plates and probed with Fat 13, Fat 37, Fat 40 and Fat 41. The ELISA methods employed for these antibodies were identical to those described in 7.4.1 above.

7.5.2 Evaluation of IEF Results

25 ELISA analysis of adipocyte plasma membrane proteins resolved by Rotorfor IEF revealed that Fat 13, Fat 37 and Fat 41 were all producing similar profiles of binding. For each of these antibodies the *pI* of the antigen was resolved over a wide pH range, from pH 5.5 to 8. Although the antigen/s bound by

30 these antibodies did not focus particularly well at first, a more accurate *pI* was obtained by performing a second Rotofor run using a narrower pH gradient, i.e. pH 5 to 8. The *pI* of the antigen recognised by Fat 37 was determined to be between pH 5.5 to 6. The antigen bound by Fat 40 focussed to a narrow pH range in the first run and the *pI* was determined as pH 6.

7.6 Summary

We have performed a preliminary characterisation of the antigens bound by four anti-adipocyte antibodies: Fat 13, Fat 37, Fat 40 and Fat 41. One benefit of such a study would be 5 the identification of important molecular characteristics for each antigen, for example molecular weight and isoelectric point. This information could then be directly applied to facilitate antigen purification and identification from the target tissue.

10

On SDS-PAGE westerns, only Fat 37 bound to its (35KDa) antigen. The other antibodies did not bind on these blots presumably because their epitopes are conformationally dependent. However, Fat 37, Fat 40 and Fat 41, but not Fat 15 13, were shown to bind their respective antigens on native westerns. On these native westerns it was apparent that Fat 37 and Fat 41 were binding to the same antigen whereas Fat 40 was binding to a different antigen.

20 A similar conclusion was drawn from the antigen stability study. In this study, the loss in binding of Fat 37 and Fat 41 to heat denatured adipocyte plasma membranes was observed at identical rates. Interestingly, Fat 13 also gave similar profiles to Fat 37 and Fat 41 in this study. However, Fat 40, 25 again, followed a different profile to the other antibodies.

The isoelectric points for each antigen were determined by IEF analysis. The pI was approximately the same for all the antigens, i.e. in the pH range 5.5 to 8. For the antigens 30 recognised by Fat 37 and Fat 40, the pI was resolved further to pH 5.5 to 6 and pH 6, respectively.

In conclusion, these characterisation studies provide 35 indication that Fat 37 and Fat 41 are binding to the same antigen and that Fat 40 is binding to a different antigen.

This conclusion is also supported by the ICC profiles observed for these antibodies: Fat 37 and Fat 41 have been shown to bind adipocytes and capillaries in many tissues whereas Fat 40 binds to adipocytes and smooth muscle. The 5 characterisation studies did not yield sufficient data on the antigen bound by Fat 13 to make any firm conclusions. However, Fat 13 has a similar ICC profile to Fat 37 and 41 and also closely follows the profiles of these antibodies in the antigen stability study. Thus it may be the case that Fat 10 13 is also binding to the same antigen as Fat 37 and Fat 41.

7.7 Antigen Identification

In order to determine the antigens bound by any of the anti-adipocyte antibodies a number of techniques could be 15 employed. These are detailed in the following section.

7.7.1 Protein purification

7.7.1.1 Detergent solublisation

Membrane proteins are generally not directly soluble in 20 aqueous solutions. In order to make the proteins soluble they must first be treated with detergents. Which detergent is useful for which protein is determined empirically. The detergent is added to a membrane preparation from human adipocytes at the CMC. The CMC is the concentration of 25 detergent above which the detergent forms micelles in aqueous solution. The membranes and detergent are then mixed extensively, if the protein can be solublised by the detergent it will be extracted from the membranes into the detergent micelles. The proteins remaining in the membrane 30 can be precipitated by ultra centrifugation leaving the detergent solublised proteins in solution. The protein can be detected by ELISA. It is unlikely that a single protein will be solublised and the detergent extraction method will 35 solublise many proteins. Further purification would then be necessary.

7.7.1.2 *Immunoprecipitation*

The detergent solubilised protein is mixed with a critical concentration of antibody, allowing the formation of an antibody-antigen complex. This complex can be recovered in a number of ways, such as centrifugation, or by capture of the antibody-antigen complex on a protein a column, or if scFv is used on an anti-tag column. It may also be possible to produce affinity columns using the antibody and capturing the antigen directly onto the column.

10

7.7.1.3 *Electrophoresis*

Proteins can be separated on the basis of their charge and size. By treating the protein with a charged detergent such as the anionic detergent SDS the protein can be made to take on charge that is independent of the charged amino acids that the protein may contain. The amount of detergent taken up by the protein is dependent on the size of the protein and separating the proteins on the basis of charge will then be directly proportional to the size of the protein. When these proteins are placed in an electric field they will migrate towards the electrode carrying the charge opposite to the overall charge carried by the protein. This is achieved by forming a matrix onto which the proteins can be loaded and through which they migrate in the electric field (Laemmli 1970, Nature Vol 227 : 680-685). Following electrophoresis they remain in the matrix where they can be visualised by direct staining, western blotting, or can be eluted for further analysis to provide information on size and composition.

30

7.7.1.4 *Amino acid sequencing*

Once the antigen of interest has been purified the sequence of amino acids that makes up the protein can be determined using Edman degredation. A chemical reaction is performed on the protein which labels the terminal amino acid at the

N-terminal end of the protein and separates it from the remainder of the protein. The amino acid separated from the protein can be identified and the process repeated. Many cycles of this are performed and the primary amino acid 5 sequence of the protein identified. [G Allen in "Sequencing of proteins and peptides" (TS Work and RH Burdon, Eds.) Elsevier, Amsterdam, New York 1981].

7.7.1.5 *Directed antigen biotinylation*

10 The size of unknown antigens can also be determined by direct biotinylation of the antigen using biotin tyramine reagent. Solubilised membranes containing the antigen are incubated with HRP conjugated antibody or antibody fragment that binds the antigen. Biotin tyramine and hydrogen peroxide are then 15 added and incubation carried out at room temp for 10 mins. An aliquot of the reactions is mixed with the appropriate volume of SDS loading buffer and heated to 95°C for 5 min. The proteins are loaded onto a 14% acrylamide SDS gel and separated by electrophoresis. The proteins are then 20 transferred to a PVDF membrane and probed with streptavidin HRP. This will bind to the proteins labelled with the biotin in the biotin tyramine reaction. Proteins can be visualised by incubation with ECL reagents (Amersham) and exposure to either photographic emulsion or the image captured on a video 25 camera system.

If specific labelling has occurred then the biotinylated proteins can be captured on a streptavidin surface of a SELDI mass spectrometer chip and the molecular weights determined. 30 Treatment of the captured proteins with trypsin or other sequence specific protease would allow peptide mass mapping to be carried out and identification of the protein through comparison to mass maps from other known proteins.

35 7.7.2 *Cloning*

7.7.2.1 cDNA library construction

The mRNA from the cell type or tissue of interest (known to co-express antigen) is converted to a DNA copy using the enzyme reverse transcriptase. This converts the mRNA strand 5 into a complementary DNA (cDNA) copy annealed to the mRNA. The RNA is then converted into DNA using a combination of the enzyme RnaseH, which introduces breaks in the RNA and DNAPolimeraseI from E.coli which recognises the breaks and removes the RNA and replaces it with DNA. The cDNA is then 10 ligated into a plasmid vector such that upstream of the cloned cDNA is a eukaryotic promoter and downstream is a transcriptional terminator. The vector should also carry a selectable marker and an origin of replication for amplification in E. coli and an origin for replication and 15 maintenance in eukaryotic cells such as the SV40 origin (eg et al. 1994, PNAS USA 91, 9228-9232).

7.7.2.2 Expression screening

A library consisting of a number of clones in the region of 1 20 $\times 10^6$ individuals is amplified in E. coli and the DNA purified. This is then used to transfect a eukaryotic cell line such as COS-7 cells (monkey kidney cells). The proteins encoded by the cDNA are expressed in the COS cells and transmembrane proteins would be present on the cell surface. 25 Using antibodies to the protein of interest the cells expressing the antigen can be labelled and separated from the unlabelled cells either by cell sorting or antibody capture. The plasmids within them can be isolated and further rounds of transfection and selection performed if necessary. Once 30 clonal plasmid encoding the antigen has been isolated the sequence of the cDNA can be determined and the amino acid sequence of the antigen deduced. An example of this type of approach was taken by Aruffo, A and Seed, B. 1987 Molecular cloning of a CD28 cDNA by a high efficiency COS cell 35 expression system (Proc. Natl. Acad. Sci. (USA) 84: 8573).

7.7.3 Summary

A number of methods are described for identifying the antigens bound by the anti-adipocyte antibodies. A combination of these allows for identification of antigen and

5 its cDNA and/or amino acid sequence. This sequence information can be analysed by searching protein databases for matches to known proteins. The results of these searches may lead to the identification of either novel adipocyte antigens or known antigens newly identified on the adipocyte

10 cell surface.

All documents identified in this specification are incorporated by reference.

Table 1

Adipose Source	Selection on Adipocyte	Round	Input Titre	Output Titre
Abdominal subcutaneous	Cell surface	1	1×10^{13}	1.25×10^7
	Plasma membrane	2	4×10^{11}	1.1×10^6
	Plasma membrane	3	5×10^{11}	2.25×10^7
Abdominal subcutaneous	Cell surface	1	4×10^{12}	3.6×10^6
	Cell surface	2	2×10^{12}	2×10^8
	Cell surface	3	1.2×10^{12}	7×10^7
Omental	Cell surface	1	4×10^{12}	1.3×10^6
	Cell surface	2	4×10^{12}	8×10^7
	Cell surface	3	1.5×10^{12}	2×10^7
Lipoma	Cell surface	1	1×10^{13}	1×10^7
	Plasma membrane	2	4×10^{11}	2×10^6
	Plasma membrane	3	5×10^{11}	1×10^8

5

10

Table 2

Adipose Source	Temp.	Selection on Adipocyte	Round	Input Titre	Output Titre
Intact adipose	4°C	Tissue	1	1×10^{13}	5×10^8
		Plasma membrane	2	1.95×10^{12}	1.9×10^5
		Plasma membrane	3	2.2×10^{13}	2.7×10^8
Intact adipose	25°C	Tissue	1	1×10^{13}	5×10^8
		Plasma membrane	2	2.8×10^{12}	5.4×10^5
		Plasma Membrane	3	1.2×10^{13}	2.2×10^8

15

Table 3

Adipose Source	Temp.	Selection on Adipocyte	Round	Input Titre	Output Titre

Abdominal subcutaneous	4 °C	Cell surface Cell surface	1 2	1x10 ¹³ 1.5x10 ¹³	3.5x10 ⁴ 2.6x10 ⁴
Abdominal subcutaneous	25 °C	Cell surface Cell surface Plasma membranes	1 2 2	1x10 ¹³ 2.2x10 ¹³ 1x10 ¹²	1.5x10 ⁵ 8x10 ⁴ 2x10 ⁴

TABLE 4

	Clone name	VH seg	VHCDR3	VL seg
5	FAT.1	VH3 DP49	NPRLAYDAFDI	VK1 DPK9
	FAT.2	VH3 DP35	GGFEELFDGSFDI	V λ 3 DPL16
	FAT.3	VH4 DP79	DRGFYGLDV	V λ 3 DPL16
	FAT.4	VH3 DP53	DMWGTMDV	V λ 3 IGLV3S2
	FAT.5	VH3 DP47	TIAYGDYGF DY	V λ 3 DPL 16
	FAT.6	VH1 DP25	DIYYGSGYAFDI	V λ 3 DPL 16
10	FAT.7	VH3 DP47	SLYRWELLDF	V λ 3 DPL 16
	FAT.8	VH3 DP49	DRRLQDAFDI	VK1 DPK9
	FAT.9	VH3 DP49	ELGFSGPFDY	VK1 DPK9
	FAT.10	VH1 DP25	FRGSGSF DV	V λ 3 DPL 16
	FAT.11	VH3 DP47	DLGTGDSNYQFY YMDV	V λ 3 DPL 16
	FAT.12	VH1 DP25	WGDFYYYMDV	VK1 DPK9
15	FAT.13	VH4 DP66	DNWGSLDY	V λ 6 IGLV6.S1
	FAT.14	VH1 DP10	GWDT	V λ 3 DPL 16
	FAT.15	VH4 DP79	YKWNTWFDP	V λ 3 DPL 16
	FAT.16	VH3 DP47	SLYRWELFDF	V λ 3 DPL 16
	FAT.17	VH3 DP47	SLFRWELFDL	V λ 3 DPL 16
	FAT.18	VH4 DP71	DGESPLDFYFDF	V λ 3 DPL 16
20	FAT.19	VH3 DP49	DSWISGNFDY	VK1 DPK9
	FAT.20	VH3 DP47	DYFDILTGPMDV	V λ 3 DPL 16
	FAT.21	VH3 DP47	GGHYYGMDV	V λ 3 DPL 16
	FAT.22	VH3 DP50	GWWSTNTYYFDY	VK1 DPK1
	FAT.23	VH1 DP7	DSGYDGHGMDV	V λ 3 DPL 16
	FAT.25	VH3 DP49	RWYGGSGYWG HFYSYMDG	V λ 3 DPL 16
25	FAT.26	VH3 DP46	YYISG	V λ 3 DPL 16
	FAT.27	VH3 DP46	YYVSG	V λ 3 DPL 16
	FAT.28	VH3 DP38	WGPPVYAKP	V λ 3 DPL 16
	FAT.29	VH4 DP67	VNRYGSPBT	V λ 3 DPL 16
	FAT.30	VH5 DP73	PHYPMTTDDAFDI	V λ 1 DPL 5/2
	FAT.31	VH3 DP31	AAIASLGNCTSASCYNGAFDI	V λ 1 DPL 5/2
30	FAT.32	VH5 DP73	TDDGYNFAFDI	V λ 1 DPL 5/2
	FAT.33	VH3 DP35	GSGLDH	V λ 1 DPL 5/2
	FAT.34	VH5 DP73	SMGTGWYVSYPDF	V λ 1 DPL 5/2
	FAT.35	VH4 DP63	DTVGDYDSGGYYY SDS	V λ 1 DPL 5/2
	FAT.36	VH1 DP14	DGVLDYYYGMDV	V λ 1 DPL 5/2
	FAT.37	VH1 DP10	NYYYDSSGYYLYDAFDI	V λ 1 DPL 5/2
35	FAT.38	VH1 DP15	WPDCSGTSCYSPNY	V λ 1 DPL 5/2
	FAT.39	VH1 DP14	YDARGYYYLDF	V λ 1 DPL 5/2
	FAT.40	VH4 DP70	GYNWHYDDAFDI	V λ 3 DPL 16
	FAT.41	VH1 DP14	EASLNWLWPDPTWAFDI	V λ 1 DPL 5/2
	FAT.42	VH1 DP14	GRAAADKTDY	V λ 1 DPL 5/2
	FAT.44	VH1 DP14	KGLDRTYYMDVWGQVES	V λ 1 DPL 5/2
40	FAT.45	VH3 DP58	GGSSPAGVADY	V λ 1 DPL 5/2
	FAT.46	VH3 DP32	SMIEGAFDI	V λ 1 DPL 5/2
	FAT.48	VH3 DP47	AYSSEDY	V λ 1 DPL 5/2
	FAT.49	VH3 DP47	GLTVFGVVNALDV	V λ 1 DPL 5/2
	FAT.50	VH2 DP26	ERDYRLDY	V λ 1 DPL 5/2

	FAT.52	VH1	DP14	SLVPTNCDN	Vλ1	DPL	5/2
	FAT.53	VH5	DP73	HDVGYCSSNCARRPEYFQH	Vλ1	DPL	5/2
	FAT.54	VH1	DP10	DASIPDDTWDY	Vλ1	DPL	5/2
	FAT.55	VH3	DP77	GQRLYIDS	Vλ1	DPL	5/2
5	FAT.56	VH6	DP74	DGSLGLDALDI	Vλ1	DPL	5/2
	FAT.57	VH1	DP10	GKYAGNSGRHGMDV	Vλ1	DPL	5/2
	FAT.58	VH3	DP35	DRDSSGYHI	Vλ1	DPL	5/2
	FAT.59	VH3	DP61	DVYGMDV	Vλ1	DPL	5/2
10	FAT.60	VH1	DP25	RSGDVDTDMITSDAVDI	Vλ1	DPL	5/2
	FAT.61	VH1	DP10	DYYDNGATNFDY	Vλ1	DPL	5/2
	FAT.62	VH3	DP35	GDGSDYYAMDY	Vλ1	DPL	5/2
	FAT.63	VH3	DP49	DGTTRTTATDYM DV	Vλ1	DPL	5/2
	FAT.64	VH1	DP15	PGGLGAARPFDY	Vλ2	DPL	10
	FAT.65	VH3	DP35	DARWFDP	Vλ1	DPL	5/2
15	FAT.66	VH3	DP77	EGIVGDGM DV	Vλ1	DPL	5/2
	FAT.67	VH1	DP14	CAGCSGGDDAFDI	Vλ1	DPL	5/2
	FAT.68	VH3	DP47	CQSISH	Vλ1	DPL	5/2
	FAT.69	VH5	DP73	LSQQLLMEDAFDI	Vλ1	DPL	5/2
	FAT.71	VH1	DP5	GGTPVVHDDAFEI	Vλ1	DPL	5/2
20	FAT.72	VH5	DP73	AGVAGGASDL	Vλ1	DPL	5/2
	FAT.73	VH5	DP73	HNMIARPYDPFDI	Vλ1	DPL	5/2
	FAT.74	VH1	DP10	DGQGRGWGRDWYFDI	Vk1	DPK	7
	FAT.75	VH3	DP47	DLISPYYYYGM DV	Vλ1	DPL	5/2
	FAT.76	VH1	DP14	GGGIRGM DA	Vλ1	DPL	5/2
25	FAT.77	VH3	DP31	EQADGPRIAVAGTGYMDV	Vλ1	DPL	5/2
	FAT.78	VH3	DP31	AGRGDY	Vλ1	DPL	5/2
	FAT.79	VH3	DP31	DRRTLTDYFDY	Vλ1	DPL	5/2
	FAT.82	VH3	DP48	DLPQYYYDSSGYYYPEYFQH	Vλ1	DPL	5/2
	FAT.84	VH3	DP49	GYGSSYGGTS	Vλ3	DPL	16
30	FAT.86	VH1	DP31	QYSGYDYWDYFDY	Vλ1	DPL	5/2
	FAT.87	VH3	DP77	SKVGGGNDY	Vλ1	DPL	5/2
	FAT.88	VH1	DP88	DYSSRRYSYFDY	Vλ1	DPL	5/2
	FAT.89	VH4	DP70	DRDTGBYFFDD	Vλ1	DPL	5/2
	FAT.90	VH3	DP47	DPYCGSAS TYHAFDL	Vλ1	DPL	5/2
35	FAT.91	VH3	DP31	DKEYSSYYFDY	Vλ1	DPL	5/2
	FAT.92	VH3	DP49	DVLIHQTYKWFDP	Vλ1	DPL	5/2
	FAT.93	VH3	DP32	DRNQYYDSGGYPDSFDI	Vλ1	DPL	5/2
	FAT.94	VH3	DP35	LGTE TIDY	Vλ1	DPL	5/2
	FAT.95	VH3	DP31	DLSAGGMDV	Vλ2	DPL	12
40	FAT.96	VH1	DP14	TGSLFDY	Vλ1	DPL	5/2
	FAT.97	VH1	DP10	DPLGTTGAFDI	Vλ2	DPL	11
	FAT.98	VH3	DP58	EADYYYGM DV	Vλ1	DPL	5/2
	FAT.99	VH3	DP47	DGE GTTGAEGQ	Vλ1	DPL	5/2
	FAT.101	VH3	DP47	AYGSEDY	Vλ1	DPL	5/2
45	FAT.102	VH3	DP54	DLNPGQGGTYYDAFDI	Vλ1	DPL	5/2
	FAT.103	VH3	YAC9	PGDSSGGMGRDY	Vλ1	DPL	5/2
	FAT.104	VH3	DP58	GSAYYDILTGS GDDAFDI	Vλ1	DPL	5/2
	FAT.105	VH1	DP10	EVIFFSEGMDV	Vλ1	DPL	2
	FAT.106	VH1	DP75	DIDDSGYQY	Vλ2	DPL	11

	FAT.107	VH3	DP47	DTYSGYDEAPTN	Vλ1	DPL	5/2
	FAT.108	VH1	DP14	AFNLGDSDYELEGDAFDI	Vλ1	DPL	5/2
	FAT.109	VH5	DP31	DISNIVLAPAATTSHFDY	Vλ1	DPL	5/2
	FAT.110	VH1	DP14	QYDIMTAYHTHGMDV	Vλ1	DPL	5/2
5	FAT.111	VH1	DP10	DSGYDSPFY	Vλ1	DPL	5/2
	FAT.112	VH3	DP35	DFDSGGNSAIFDI	Vλ1	DPL	5/2
	FAT.113	VH1	DP88	CAEFCSDSNCPPLDP	Vλ1	DPL	5/2
	FAT.114	VH3	DP49	DIAEGVGYYYYMNV	Vλ1	DPL	5/2
	FAT.115	VH3	DP47	RANYYYLDV	Vλ3	DPL	16
10	FAT.116	VH3	VH3-8	GGTQCSFGVCATGG	Vλ1	DPL	5/2
	FAT.117	VH1	DP14	GGFCLNPVCYHGG	Vλ1	DPL	5/2
	FAT.118	VH3	DP54	GGLPCPCAACCSGG	Vλ1	DPL	5/2

Where ND = Not determined

15 VH seg/VL seg = Closest germline VH/VL segment

Table 5

	Clone name	VH SEQ ID NO. (amino acid)	VL SEQ ID NO. (amino acid)
5	FAT.1	2	4
	FAT.2	6	8
	FAT.3	10	8
	FAT.4	12	14
	FAT.5	16	18
	FAT.6	20	22
10	FAT.7	24	26
	FAT.8	28	4
	FAT.9	30	4
	FAT.10	32	26
	FAT.11	34	36
	FAT.12	38	40
15	FAT.13	42	44
	FAT.14	46	26
	FAT.15	48	26
	FAT.16	50	26
	FAT.17	52	54
	FAT.18	56	26
20	FAT.19	58	4
	FAT.20	60	62
	FAT.21	64	26
	FAT.22	66	68
	FAT.23	70	26
	FAT.25	72	26
25	FAT.26	74	8
	FAT.27	76	8
	FAT.28	78	26
	FAT.29	80	26
	FAT.30	82	84
	FAT.31	86	88
30	FAT.32	90	84
	FAT.33	92	84
	FAT.34	94	84
	FAT.35	96	84
	FAT.36	98	84
	FAT.37	100	102
35	FAT.38	104	88
	FAT.39	106	84
	FAT.40	108	36
	FAT.41	110	84
	FAT.42	112	88
	FAT.44	114	116
40	FAT.45	118	84
	FAT.46	120	116
	FAT.48	122	84
	FAT.49	124	84
	FAT.50	126	84
	FAT.52	128	84

	FAT.53	130	84
	FAT.54	132	84
	FAT.55	134	84
	FAT.56	136	84
5	FAT.57	138	84
	FAT.58	140	84
	FAT.59	142	84
	FAT.60	144	84
	FAT.61	146	84
10	FAT.62	148	84
	FAT.63	150	84
	FAT.64	152	154
	FAT.65	156	84
	FAT.66	158	84
15	FAT.67	160	84
	FAT.68	162	84
	FAT.69	164	84
	FAT.71	166	84
	FAT.72	168	170
20	FAT.73	172	84
	FAT.74	174	176
	FAT.75	178	84
	FAT.76	180	84
	FAT.77	182	88
25	FAT.78	184	84
	FAT.79	186	84
	FAT.82	188	84
	FAT.84	190	26
	FAT.86	192	84
30	FAT.87	194	84
	FAT.88	196	84
	FAT.89	198	84
	FAT.90	200	84
	FAT.91	202	84
35	FAT.92	204	84
	FAT.93	206	84
	FAT.94	208	84
	FAT.95	210	212
	FAT.96	214	84
40	FAT.97	216	218
	FAT.98	220	88
	FAT.99	222	224
	FAT.101	226	116
	FAT.102	228	84
45	FAT.103	230	84
	FAT.104	232	84
	FAT.105	234	236
	FAT.106	238	240
	FAT.107	242	84
50	FAT.108	244	84
	FAT.109	246	84

82

	FAT.110	248	84
	FAT.111	250	88
	FAT.112	252	254
	FAT.113	256	258
5	FAT.114	260	84
	FAT.115	262	264
	FAT.116	266	88
	FAT.117	268	84
	FAT.118	270	84

10

Table 6

Clone Number	Adipose	Spleen	Heart	Kidney	Colon	Lung	Skin	Striated Muscle	Tonsil	Testis
1	+	+	+	-	-	+	-	-	-	-
3	+	-	nd	+	+	+	+	-	+	+
4	+	-	nd	-	-	+	-	+	-	+
5	+	+	nd	-	-	-	-	-	-	-
6	+	-	nd	-	+	+	-	+	-	-
8	+	+	nd	nd	nd	nd	nd	nd	nd	nd
10	+	-	nd	-	-	+	-	-	-	-
12	+	-	nd	-	+	-	+	-	-	-
13	+	-	+	-	-	-	-	+	-	+
15	+	-	nd	+	-	+	-	-	+	-
16	+	-	nd	+	+	+	-	-	-	-
17	+	-	nd	+	-	+	+	-	+	+
19	+	+	nd	nd	nd	nd	nd	nd	nd	nd
20	+	+	nd	nd	nd	nd	nd	nd	nd	nd
22	+	-	nd	-	+	+	+	+	-	+
23	+	+	nd	-	+	+	-	-	-	-
24	+	-	nd	-	+	+	-	-	-	-
26	+	+	+	-	+	-	-	-	-	-
27	+	+	nd	-	+	-	-	-	-	-
29	+	-	nd	-	+	-	+	-	+	-
30	+	+	nd	+	nd	nd	nd	nd	nd	nd
31	+	+	nd	+	+	+	-	+	-	+
32	+	-	nd	+	+	-	+	-	+	-
34	+	-	nd	+	-	-	-	-	+	-
36	+	+	nd	+	+	-	+	-	-	-
37	+	-	+	-	+	+	-	+	-	+
38	+	-	nd	-	+	-	-	-	-	-
39	+	+	nd	-	+	+	-	+	-	+
40	+	+	+	+	+	+	+	-	+	+
41	+	+	nd	+	+	+	-	+	-	+
42	+	+	nd	-	+	+	-	-	+	-
44	+	+	nd	-	+	-	-	-	-	-
46	+	-	nd	-	+	-	-	+	-	-

Clone Number	Adipose	Spleen	Heart	Kidney	Colon	Lung	Skin	Striated Muscle	Tonsil	Testis
48	+	-	nd	-	-	-	+	-	-	-
52	+	-	nd	+	-	-	-	+	-	-
57	+	-	+	-	-	-	-	-	-	-
58	+	-	+	-	-	-	-	-	-	-
60	+	-	nd	-	+	-	+	+	-	-
61	+	-	+	-	-	-	-	-	-	-
63	+	-	nd	+	-	-	-	-	-	-
67	+	-	+	-	-	-	-	-	-	-
68	+	+	nd	+	-	-	-	-	-	-
71	+	-	nd	+	-	-	+	+	-	-
72	+	+	nd	-	+	-	-	+	-	-
73	+	+	+	-	-	-	-	-	-	-
75	+	-	+	-	-	-	-	-	-	-
76	+	-	+	-	-	-	-	-	-	-
77	+	+	nd	-	+	+	+	+	-	+
78	+	+	nd	-	-	-	-	-	-	-
79	+	+	nd	-	-	-	-	-	-	-
80	+	+	nd	-	-	-	+	-	-	-
82	+	-	+	-	-	-	-	-	-	-
84	+	+	nd	-	-	-	-	-	-	-
86	+	-	+	-	-	-	+	-	-	-
87	+	+	nd	-	-	-	+	-	-	-
89	+	-	+	-	-	-	-	-	-	-
90	+	+	nd	-	-	-	+	-	-	-
91	+	+	nd	-	-	-	-	-	-	-
92	+	-	+	-	-	-	-	-	-	-
93	+	+	nd	-	-	-	-	-	-	-
94	+	+	nd	-	-	-	+	-	-	-
96	+	-	+	+	-	-	-	-	-	-
97	+	-	+	-	-	-	-	+	-	-
98	+	+	nd	-	+	+	+	+	-	+
99	+	+	nd	+	-	-	-	+	-	-
101	+	+	nd	+	-	-	-	+	-	-

Clone Number	Adipose	Spleen	Heart	Kidney	Colon	Lung	Skin	Striated Muscle	Tonsil	Testis
102	+	-	+	+	-	-	-	+	-	-
103	+	-	+	+	-	-	+	+	-	+
104	+	-	+	+	+	-	-	+	-	-
106	+	-	+	-	-	-	+	+	-	-
107	+	-	+	+	-	-	-	-	-	-
108	+	-	+	+	-	-	-	+	-	-
109	+	+	+	+	-	-	-	+	-	-
110	+	-	nd	+	-	-	+	-	-	-
111	+	+	nd	+	+	-	+	+	-	-
113	+	+	nd	-	-	-	-	+	-	-
114	+	+	+	-	-	-	-	-	-	-
115	+	-	nd	+	+	-	+	-	-	-
116	+	+	nd	+	+	-	-	+	-	-
117	+	-	nd	+	-	-	-	-	-	-
118	+	-	nd	+	-	-	-	+	-	-

+= positive staining, - = no staining observed and nd = not determined

*ANTIBODY VH AND VL DOMAIN AMINO ACID SEQUENCES AND CODING
NUCLEOTIDE SEQUENCES*

The cDNA and amino acid sequences of 108 anti-adipocyte
5 antibodies according to embodiments of the present invention
are detailed in this section. For each antibody, heavy chain
sequence information is detailed first followed by the light
chain sequence information. In the heavy chain amino acid
sequences the CDR3 is underlined. A number of the anti-
10 adipocyte antibodies share light chains in common: the
sequences for these are not duplicated but are cross-
referenced to each other.

CLAIMS

1. A library or panel of at least 10 different specific binding members, the library or panel comprising specific binding members each able to bind whole adipocytes and each comprising an antibody VH variable domain, wherein each antibody VH variable domain comprises a VH CDR shown in Table 4 and optionally has an amino acid sequence selected from the group consisting of those with a SEQ ID NO. listed in Table 5.
2. A library or panel according to claim 1 comprising at least 100 different antibody VH CDR's or antibody VH variable domains.
3. A library or panel according to claim 2 comprising or consisting of all 108 different VH domains of which the amino acid SEQ ID NO.'s are listed in Table 5.
4. A library or panel according to claim 2 comprising or consisting of all 108 different VH CDR3's shown in Table 4.
5. A library or panel according to any one of claims 1 to 4 wherein each VH domain is paired with a VL domain.
6. A library or panel according to claim 5 wherein the VL domain is or VL domains in the library or panel are selected from the group consisting of those of which the amino acid sequence has a SEQ ID NO. listed in Table 5.
7. A library or panel according to claim 6 wherein one or more VL domains in the library or panel is or are selected from the group consisting of those with SEQ ID NO.'S 4, 8, 26, 84, 88 and 116.

8. A method of obtaining one or more specific binding members able to bind an adipocyte antigen, the method including bringing into contact a library or panel of specific binding members according to any one of claims 1 to 5 7 and said adipocyte antigen, and selecting one or more specific binding members of the library or panel able to bind said adipocyte antigen.

9. A method according to claim 8 wherein specific binding members in the library or panel are displayed on the surface 10 of bacteriophage particles, each bacteriophage particle containing nucleic acid encoding the antibody VH variable domain displayed on its surface, and optionally also a displayed VL domain if present.

15 10. A method according to claim 9 wherein bacteriophage particles displaying a specific binding member able to bind said adipocyte antigen are selected, and nucleic acid is taken from such a selected bacteriophage particle.

20 11. A method according to claim 10 wherein said nucleic acid is used in subsequent production of a specific binding member or an antibody VH variable domain, and optionally an antibody VL variable domain, by expression from nucleic acid with the 25 sequence of nucleic acid taken from a selected bacteriophage particle displaying a specific binding member able to bind said adipocyte antigen.

12. A method according to any one of claims 8 to 11 30 comprising provision of a selected specific binding member or antibody VH domain of a selected specific binding member in isolated form.

13. A method according to any one of claims 8 to 11 35 comprising provision of a plurality of selected specific

binding members or antibody VH domains of a selected specific binding members in isolated form.

14. A method according to claim 13 comprising provision of a
5 mixture of selected specific binding members or antibody VH domains of selected specific binding members in isolated form.

15. A method according to any one of claims 12 to 15 wherein
10 a selected specific binding member or an antibody VH variable domain of a selected specific binding member optionally with a VL domain, a plurality of said specific binding members or antibody VH variable domains optionally with VL domains, or a mixture of said specific binding members or antibody VH
15 variable domains optionally with VL domains, in isolated form is formulated into a composition including at least one additional component.

16. A method according to any one of claims 8 to 15 wherein
20 a selected specific binding member or VH domain of a selected specific binding member is provided in a fusion protein with additional amino acids.

17. A method according to claim 16 wherein said additional
25 amino acids provide an antibody constant region.

18. A mixture of 10 different specific binding members each comprising an antibody VH variable domain, obtainable from a library according to any one of claims 1 to 6, wherein each
30 antibody VH variable domain has an amino acid sequence selected from the group consisting of the VH domains of Fat3 (SEQ ID NO. 10), Fat13 (SEQ ID NO. 42), Fat17 (SEQ ID NO. 52), Fat31 (SEQ ID NO. 86), Fat37 (SEQ ID NO. 100), Fat40 (SEQ ID NO. 108), Fat86 (SEQ ID NO. 192), Fat97 (SEQ ID NO. 216), Fat103 (SEQ ID NO. 230) and Fat106 (SEQ ID NO. 238).

19. A mixture of 10 different specific binding members each comprising an antibody VH variable domain, obtainable from a library according to any one of claims 1 to 6, wherein each antibody VH variable domain has an amino acid sequence

5 comprising a CDR3 selected from the group consisting of the VH domains of Fat3, Fat13, Fat17, Fat31, Fat37, Fat40, Fat86, Fat97, Fat103 and Fat106 (the CDR3 sequences being shown in Table 4).

10 20. A composition comprising a plurality of different antibody VH variable domains obtainable from a mixture according to claim 18 or claim 19.

15 21. A composition according to claim 20 comprising any one or more of the antibody VH variable domains of Fat3 (SEQ ID NO. 10), Fat13 (SEQ ID NO. 42), Fat17 (SEQ ID NO. 52), Fat31 (SEQ ID NO. 86), Fat37 (SEQ ID NO. 100), Fat40 (SEQ ID NO. 108), Fat86 (SEQ ID NO. 192), Fat97 (SEQ ID NO. 216), Fat103 (SEQ ID NO. 230) and Fat106 (SEQ ID NO. 238).

20 22. A composition according to claim 21 comprising either or both of the antibody VH variable domains of Fat13 (SEQ ID NO. 42) and Fat40 (SEQ ID NO. 108).

25 23. A composition according to any one of claims 18 to 22 wherein one or more of said antibody VH variable domains is in a fusion with additional amino acids.

30 24. A composition according to any one of claims 18 to 23 wherein one or more of said antibody VH variable domains is in association with an antibody VL variable domain.

35 25. An antibody VH variable domain obtainable from a library or panel according to claim 3 and having an amino acid sequence of which the SEQ ID NO. is shown in Table 5.

26. An antibody VH variable domain obtainable from a mixture according to claim 18.

5 27. An antibody VH variable domain obtainable from a mixture according to claim 19.

28. A specific binding member comprising an antibody VH variable domain according to claim 26 or claim 27 and an antibody VL variable domain.

10

29. Nucleic acid encoding an antibody VH variable domain according to claim 26 or claim 27.

15

30. Nucleic acid encoding a specific binding member according to claim 28.

31. A host cell transformed with such nucleic acid according to claim 29 or claim 30.

20 32. A method of producing an antibody VH variable domain or specific binding member, the method comprising culturing host cells according to claim 31 under conditions for production of said antibody VH variable domain or specific binding member.

25

33. A method according to claim 32 further comprising isolating and/or purifying said antibody VH variable domain or specific binding member.

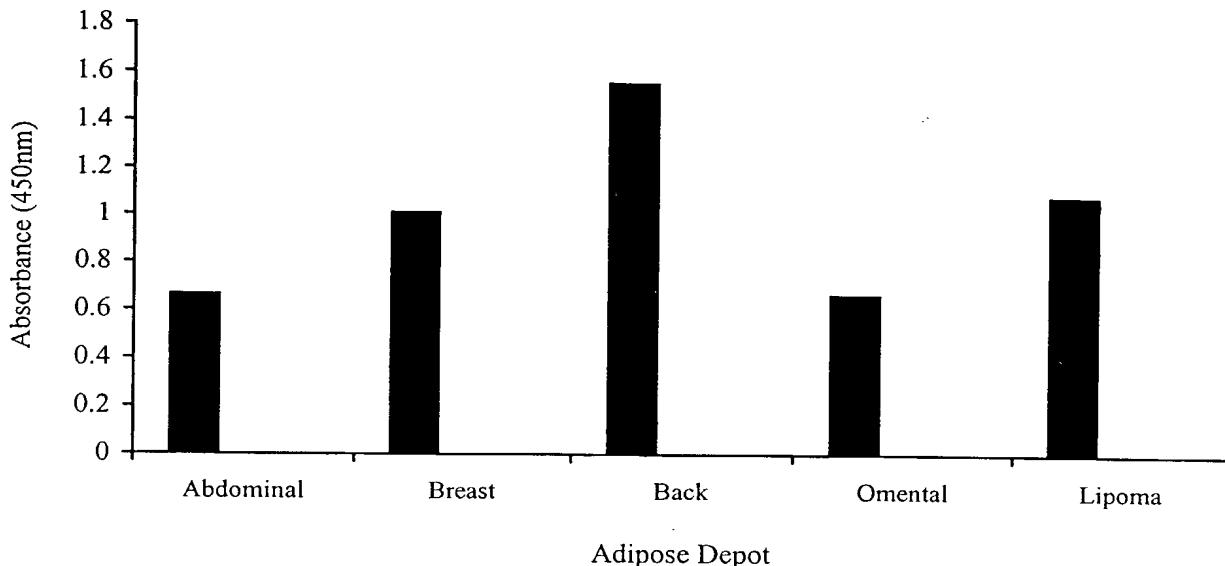
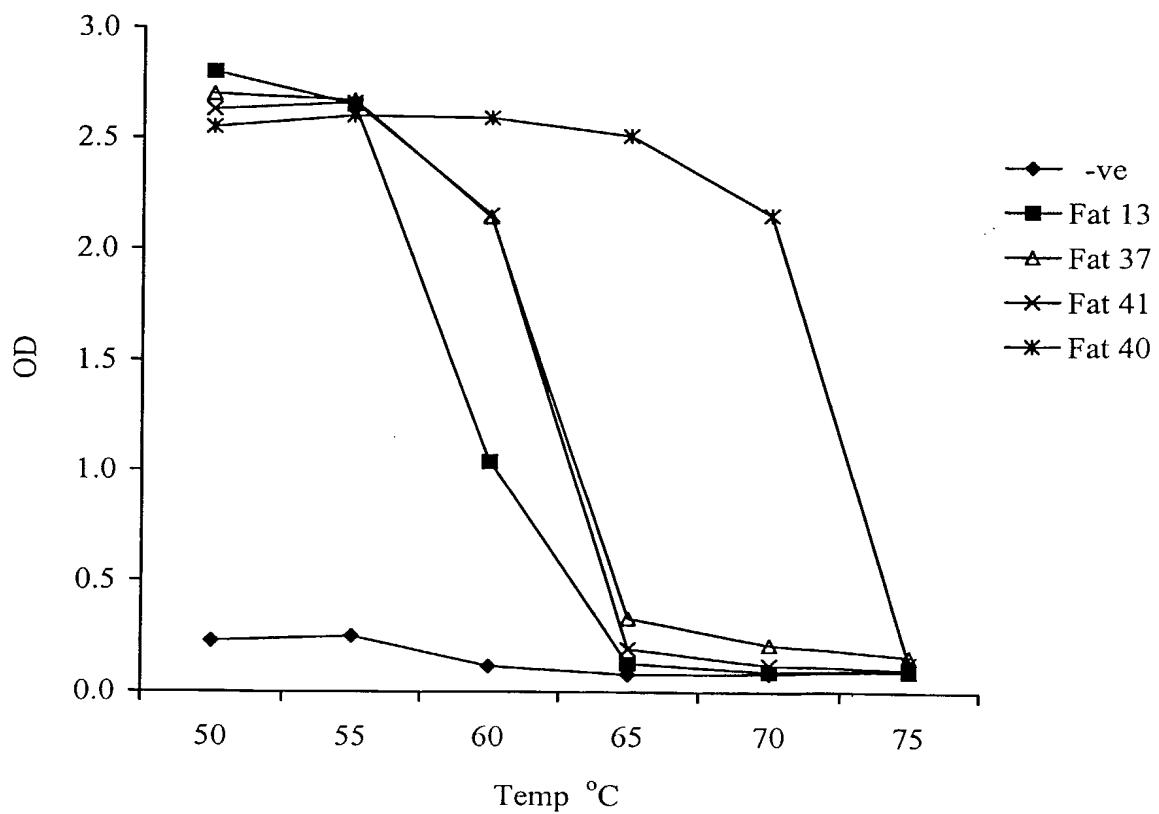
30 34. A method according to claim 32 or claim 33 further comprising formulating the said antibody VH variable domain or specific binding member into a composition including at least one additional component.

35. A method of obtaining one or more antigen molecules, the method comprising bringing into contact material suspected of containing an antigen of interest and a specific binding member or plurality or mixture of specific binding members as 5 claimed in a preceding claim, and selecting one or more antigen molecules bound by said specific binding member, plurality or mixture thereof.

36. A method according to claim 35 further comprising 10 providing a selected antigen molecule in an isolated and/or purified form.

37. A method according to claim 36 further comprising formulating said selected antigen molecule into a composition 15 including at least one additional component.

1/1

Figure 1**Figure 2**

FAT 1 Heavy Chain DNA sequence SEQ ID NO. 1

CAGGTGCAGCTGGTGCAGTCTGGGGAGGCCTGGTCCAGCCTGGGAGGTCCCTGAGACTCT
 5 CCTGTGCAGCCTCTGGATTACCTTCAGTAGCTATGGCATGCACGGTCCGCCAGGCTCC
 AGGCAAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTATTAAATACTATGCA
 GACTCCGTGAAGGGCCGATTACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGC
 AAATGAACAGCCTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGCAAACCCAGACT
 GGCCTATGATGCTTTGATATCTGGGCCAGGGACAATGGTCACCGTCTCTCA

10

FAT 1 Heavy Chain Amino Acid sequence SEQ ID NO. 2

Q	V	Q	L	V	Q	S	G	G	G	V	V	Q	P	G	R	S	L	R	L	S	
C	A	A	S	G	F	T	F	S	S	Y	G	M	H	W	V	R	Q	A	P	G	
15	K	G	L	E	W	V	A	V	I	S	Y	D	G	S	I	K	Y	Y	A	D	S
V	K	G	R	F	T	I	S	R	D	N	S	K	N	T	L	Y	L	Q	M	N	
S	L	R	A	E	D	T	A	V	Y	Y	C	A	R	<u>N</u>	<u>P</u>	<u>R</u>	<u>L</u>	<u>A</u>	<u>Y</u>	<u>D</u>	
<u>A</u>	<u>F</u>	<u>D</u>	<u>I</u>	<u>W</u>	<u>G</u>	<u>Q</u>	<u>G</u>	<u>T</u>	<u>M</u>	<u>V</u>	<u>T</u>	<u>V</u>	<u>S</u>	<u>S</u>							

20

FAT 1 Light Chain DNA sequence SEQ ID NO. 3

GACATCGTGATGACCCAGTCTTTCCACCCCTGTCTGCATCTGTAGGAGACAGAGTCACCA
 TCACTTGCAGGGCCAGTCAGGGTATTAGTAGCTGGTTGGCCTGGTATCAGCAGAAACCAGG
 GAGAGCCCCTAAGGTCTTGATCTATAAGGCATCTACTTAGAAAGTGGGTCCCATCAAGG
 25 TTCAGCGGCAGTGGATCTGGACAGATTCACTCTCACCATCAGCAGTCTGCAACCTGAAG
 ATTTTGCAACTTACTACTGTCAACAGAGTTACAGTACCCGTGGACGTTGGCCAAGGGAC
 CAAGCTGGAGATCAAACGTGCGGCCGCACATCATCACCATCAC

FAT 1 Light Chain Amino Acid sequence SEQ ID NO. 4

30

D	I	V	M	T	Q	S	L	S	T	L	S	A	S	V	G	D	R	V	T	I
T	C	R	A	S	Q	G	I	S	S	W	L	A	W	Y	Q	Q	K	P	G	R
A	P	K	V	L	I	Y	K	A	S	T	L	E	S	G	V	P	S	R	F	S
G	S	G	S	G	T	D	F	T	L	T	I	S	S	L	Q	P	E	D	F	A

2

T	Y	Y	C	Q	Q	S	Y	S	T	P	W	T	F	G	Q	G	T	K	L	E
I	K	R	A	A	A															

FAT 2 Heavy Chain DNA sequence SEQ ID NO. 5

5 CAGGTGCAGCTGCAGGAGTCGGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCTGAGACTCT
 CCTGTACAGCCTCTGGATTGCCTTCAGTGACCACTACATGAGTTGGGTCCGCCAGGCTCC
 AGGGAAGGGCTGGAGTGGATTCATCCATTAGTACGAGTAGTATGTATATAAATTATGCA
 GACTCTGTGAAGGGCCGATTCAACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGC
 10 AAATGAACAGCCTGAGAGCTGAGGACACGGCTGTGTATTCTGTGTTTGGGGGATTGCA
 AGAATTATTTGATGGTTCTTTGATATCTGGGCCAAGGCACCCCTGGTCACCGTCTCGAGT

FAT 2 Heavy Chain Amino Acid sequence SEQ ID NO. 6

15	Q	V	Q	L	Q	E	S	G	G	R	L	G	Q	A	W	R	V	L	R	L	S	
	C	T	A	S	G	F	A	F	S	D	H	Y	M	S	W	V	R	Q	A	P	G	
	K	G	L	E	W	I	S	S	I	S	T	S	S	M	Y	I	N	Y	A	D	S	
	V	K	G	R	F	T	I	S	R	D	N	S	K	N	T	L	Y	L	Q	M	N	
	S	L	R	A	E	D	T	A	V	Y	F	C	V	L	<u>G</u>	<u>G</u>	<u>F</u>	<u>E</u>	<u>E</u>	<u>L</u>	<u>F</u>	
20	<u>D</u>	<u>G</u>	<u>S</u>	<u>F</u>	<u>D</u>	<u>I</u>	<u>W</u>	<u>G</u>	<u>Q</u>	<u>G</u>	<u>T</u>	<u>L</u>	<u>V</u>	<u>T</u>	<u>V</u>	<u>S</u>	<u>S</u>					

FAT 2 Light Chain DNA sequence SEQ ID NO. 7

25 TCTTCTGAGCTGACTCAGGACCCTGCTGTGTCTGTGGCCTTGGGACAGACAGTCAGGATCA
 CTTGCCAAGGAGACAGTCTCAGAACAGTATTACACAAACTGGTCCAGCAGAACGCCAGGACA
 GGCCCCTCTACTTGTGTCTATGCTAAAAACAACCGGCCCTCAGGGATCCCAGACCGATTC
 TCTGGCTCCAGCTCAGGAAACACAGCTTCCTGACCATCACTGGGCTCAGGCGGAAGATG
 AGGCTGACTATTACTGTAACCTCCGGGACAGCAGTGGTAACCATGTGGTATTGGCGGGAGG
 GACCAAGCTGACCGTCCTAGGTGCGGCCGCACATCATCACCATCAC

30

FAT 2 Light Chain Amino Acid sequence SEQ ID NO. 8

35	S	S	E	L	T	Q	D	P	A	V	S	V	A	L	G	Q	T	V	R	I	T
	C	Q	G	D	S	L	R	S	Y	Y	T	N	W	F	Q	Q	K	P	G	Q	A
	P	L	L	V	V	Y	A	K	N	N	R	P	S	G	I	P	D	R	F	S	G

3

S S S G N T A S L T I T G A Q A E D E A D
Y Y C N S R D S S G N H V V F G G G T K L
T V L G

5 FAT 3 Heavy Chain DNA sequence SEQ ID NO. 9

CAGGTACAGCTGCAGCAGTCAGGCCAGGGCGGGTGAAGCCTCGGAGACCCTGTCCCTCA
CATGCTCTGTCTGGTACTCCATCAGCAGTAGTAGTCACTACTGGAGCTGGATCCGCCA
GCCGCCAGGAAAGGGCTGGAATGGATTGGCGATGTCAATCATGGTGGAAATACCAACTAC
10 AACCCGTCCCTCAAGAGTCGAGTCACCATATCAGTAGACACGTCCAAGAACCAAGTTCTCCC
TGAACCTGAAGTCTGTGACCGCCCGGACACGGCTGTGTATTACTGTGCGAGAGACCGGGG
TTTCTACGGTTGGACGTCTGGGCCAGGGCACCCCTGGTACCGTCTCGAGT

FAT 3 Heavy Chain Amino Acid sequence SEQ ID NO. 10

15

	Q	V	Q	L	Q	Q	S	G	P	G	R	V	K	P	S	E	T	L	S	L	T
	C	S	V	S	G	D	S	I	S	S	S	S	H	Y	W	S	W	I	R	Q	P
	P	G	K	G	L	E	W	I	G	D	V	N	H	G	G	N	T	N	Y	N	P
	S	L	K	S	R	V	T	I	S	V	D	T	S	K	N	Q	F	S	L	N	L
20	K	S	V	T	A	A	D	T	A	V	Y	Y	C	A	R	<u>D</u>	R	G	F	Y	G
	L	D	V	W	G	Q	G	T	L	V	T	V	S	S							

FAT 3 Light Chain DNA and Amino Acid sequences

25 Identical to FAT 2 (SEQ ID NO.'s 7 and 8)

FAT 4 Heavy Chain DNA sequence SEQ ID NO. 11

30 CAGGTGCAGCTGCAGGAGTCCGGGGAGGCTTGGTCAGCCTGGGGGTCCTGAGACTCT
CCTGTGCAGCCTCTGGATTCACCTCAGTCCCTATTGGATGCACTGGTCCGCCAAGTTCC
AGGGAAAGGGCTGGAGTGGGTCTCACGTATAAATCCTGATGGAGTAACACAGACTACGCG
GACTCCGTGAGGGGCCGATTCACCATGTCCAGAGACAACGCCAAGAACACGTTGTCTCTAG
AAATGAACAGTCTGAGAGCCGAGGGACACGGCTGTATATTTTGTGCAAGAGATATGTGGGG
GACCATGGACGTCTGGGGCCGAGGGACAATGGTCACCGTCTCGAGT

35

FAT 4 Heavy Chain Amino Acid sequence SEQ ID NO. 12

Q	V	Q	L	Q	E	S	G	G	G	L	V	Q	P	G	G	S	L	R	L	S	
C	A	A	S	G	F	T	L	S	P	Y	W	M	H	W	V	R	Q	V	P	G	
5	K	G	L	E	W	V	S	R	I	N	P	D	G	S	N	T	D	Y	A	D	S
V	R	G	R	F	T	M	S	R	D	N	A	K	N	T	L	S	L	E	M	N	
S	L	R	A	E	D	T	A	V	Y	F	C	A	R	D	M	W	G	T	M	D	
V	W	G	R	G	T	M	V	T	V	S	S										

10 FAT 4 Light Chain DNA sequence SEQ ID NO. 13

CTGCCTGTGCTGACTCAGCCCCCTCGGTGTCAGTGGCCCCAGGAAAGACGGCCACCATTA
 CCTGTGGGGAAACAAGATTGGAAGTAAAAGTGTGCATTGGTACCAGCAGCGGCCAGGCCA
 GGCCCCTGTGGTGGTCATGTATTATGATAGTGTGACGATGCTTGAGCGATTCTCTGGCTCC
 15 AATTCCGGAAACACGGCCTCCCTGACCATCACCAACGTCGAAGCCGGGGATGAGGCCGACT
 ATTACTGTCAGGTGTGGCGTAGTGATACTGATCATGTGATATTGGCGGAGGGACCAAGGT
 CACCGTCCCTAGGTGCGGCCGCACATCATCATCACCATCAC

20 FAT 4 Light Chain Amino Acid sequence SEQ ID NO. 14

L	P	V	L	T	Q	P	P	S	V	S	V	A	P	G	K	T	A	T	I	T	
C	G	G	N	K	I	G	S	K	S	V	H	W	Y	Q	Q	R	P	G	Q	A	
P	V	V	V	M	Y	Y	D	S	V	T	M	L	E	R	F	S	G	S	N	S	
G	N	T	A	S	L	T	I	T	N	V	E	A	G	D	E	A	D	Y	Y	C	
25	Q	V	W	R	S	D	T	D	H	V	I	F	G	G	G	T	K	V	T	V	L
	G																				

20 FAT 5 Heavy Chain DNA sequence SEQ ID NO. 15

30 GAGGTGCAGCTGGTGGAGTCTGGGGAGGCTTGGTACAGCCTGGGAAGTCCCTGAGACTCT
 CTTGTGCAGGCTCTGGATTCACCTTAGTAGCTATGCCATGAGTTGGTCCGTCAAGCTCC
 AGGGAAAGGGGCTGGAGTGGGTCTCAGGTATTAGTGGTAGTGGTGGTAGCACATACTACACA
 GACTCCGTGAAGGGCCGGTCAACCATCTCAGAGACAATTCCAAGAACACGCTGTATCTGC
 AAATGAACAGCCTGAGAGCTGACGACACGGCCGTATATTACTGTGCGAAAACGATCGCCTA
 35 CGGTGACTATGGCTTACTACTGGGGCCGAGGAACCTGGTCACCGTCTCCTCA

FAT 5 Heavy Chain Amino Acid sequence SEQ ID NO. 16

	E	V	Q	L	V	E	S	G	G	L	V	Q	P	G	K	S	L	R	L	S	
5	C	A	G	S	G	F	T	F	S	S	Y	A	M	S	W	V	R	Q	A	P	G
	K	G	L	E	W	V	S	G	I	S	G	S	G	G	S	T	Y	Y	T	D	S
	V	K	G	R	F	T	I	S	R	D	N	S	K	N	T	L	Y	L	Q	M	N
	S	L	R	A	D	D	T	A	V	Y	Y	C	A	K	<u>T</u>	<u>I</u>	<u>A</u>	<u>Y</u>	<u>G</u>	<u>D</u>	<u>Y</u>
	<u>G</u>	<u>F</u>	<u>D</u>	<u>Y</u>	<u>W</u>	<u>G</u>	<u>R</u>	<u>G</u>	<u>T</u>	<u>L</u>	<u>V</u>	<u>T</u>	<u>V</u>	<u>S</u>	<u>S</u>						

10

FAT 5 Light Chain DNA sequence SEQ ID NO. 17

TCGTCTGAGCTGACTCAGGACCCTGCTGTCTGTGGCCTGGGACAGACAGTCAGGATCA
 CATGCCAAGGAGACAGCCTCAGAAAGCTATTATGCAAGCTGGTACCGAGCAGAACCCAGGACA
 15 GGCCCCTGTACTTGTCACTATGGTAAAAACAACCGGCCCTCAGGGATCCCAGACCGATTCT
 TCTGGCTCCAGCTCAGGAAACACAGCTTCCTTGACCATCACTGGGCTCAGGCAGGAAGATG
 AGGCTGACTATTACTGTAACCTCCGGGACAGCAGTGGTAACCATGTGGTATTGGCCAAGG
 GACCAAGCTGGAGATCAAACGTGCGGCCGCACATCATCACACCACATCAC

20 FAT 5 Light Chain Amino Acid sequence SEQ ID NO. 18

	S	S	E	L	T	Q	D	P	A	V	S	V	A	L	G	Q	T	V	R	I	T
	C	Q	G	D	S	L	R	S	Y	Y	A	S	W	Y	Q	Q	K	P	G	Q	A
	P	V	L	V	I	Y	G	K	N	N	R	P	S	G	I	P	D	R	F	S	G
25	S	S	S	G	N	T	A	S	L	T	I	T	G	A	Q	A	E	D	E	A	D
	Y	Y	C	N	S	R	D	S	S	G	N	H	V	V	F	G	Q	G	T	K	L
	E	I	K	R																	

FAT 6 Heavy Chain DNA Sequence SEQ ID NO. 19

30

GAAGTGCAGCTGGTGCAGTCTGGGCTGAGGTGAAGAAGCCTGGGCTTCAGTGACGGTCT
 CCTGCAAGGCTTCTGGTTACACCTTACAGTTCTGGATCAACTGGGTGCGACAGGCC
 TGGACAAGGGCTTCAGTGGATGGGATCAACGCTGCCAATGGTAAAACAACATACTCA
 CAGAACCTCCAGGACAGACTCACCATTACCAGGGACGCCCTCGCGAGCACAGCCTACCTGG

AACTGAGCAGCCTGCGATCTGAAGACACGGCTGTGTATTACTGTGCGAGAGATATACTATGGTCGGG

FAT 6 Heavy Chain Amino Acid sequence SEQ ID NO. 20

5	E	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	A	S	V	T	V	S	
	C	K	A	S	G	Y	T	F	T	S	S	G	I	N	W	V	R	Q	A	P	G	
	Q	G	L	Q	W	M	G	W	I	N	A	A	N	G	K	T	T	Y	S	Q	N	
	F	Q	D	R	L	T	I	T	R	D	A	S	A	S	T	A	Y	L	E	L	S	
	S	L	R	S	E	D	T	A	V	Y	Y	C	A	R	<u>D</u>	<u>I</u>	<u>Y</u>	<u>Y</u>	G	S	G	
10	<u>Y</u>	<u>A</u>	<u>F</u>	<u>D</u>	<u>I</u>	<u>W</u>	<u>G</u>	<u>R</u>	<u>G</u>	<u>T</u>	<u>T</u>	<u>V</u>	<u>T</u>	<u>V</u>	<u>S</u>	<u>S</u>						

FAT 6 Light Chain DNA sequence SEQ ID NO. 21

	CAGTCTGTGCTGACTCAGGACCCTGCTGTGTCTGTGGCCTGGGACAGACAGTCAGGATCA
15	CATGCCAAGGAGACAGCCTCAGAACAGCTATTATGCAAGCTGGTACCAGCAGAACGCCAGGACA
	GGCCCCTGTACTTGTCTATGGTAAAAATAAGCGGCCCTCAGGGATCCAGACCGATTC
	TCTGGCTCCAGCTCAGGAAACACAGCTTCCTTGACCATCACTGGGCTCAGGCGGAAGATG
	AGGCTGACTATTACTGTCATTCCCGGGACGGCAGTGGTAACCATGTGCTTTCGGCGGAGG
	GACCAAGCTGACCGTCCTAGGT

20

FAT 6 Light Chain Amino Acid sequence SEQ ID NO. 22

	Q	S	V	L	T	Q	D	P	A	V	S	V	A	L	G	Q	T	V	R	I	T
	C	Q	G	D	S	L	R	S	Y	Y	A	S	W	Y	Q	Q	K	P	G	Q	A
25	P	V	L	V	I	Y	G	K	N	K	R	P	S	G	I	P	D	R	F	S	G
	S	S	S	G	N	T	A	S	L	T	I	T	G	A	Q	A	E	D	E	A	D
	Y	Y	C	H	S	R	D	G	S	G	N	H	V	L	F	G	G	G	T	K	L
	T	V	L	G																	

30 FAT 7 Heavy Chain DNA Sequence SEQ ID NO. 23

	CAGGTGCAGCTGGTGGAGTCTGGGGAGGCTTGGTACAGCCTGGGGGTCCCTGAGACTCT
	CCTGTGCAGCCTCTGGATTACCTTACGCTATGCCATGAGCTGGTCCGCCAGGCTCC
	AGGGAAGGGGCTGGAGTGGGTCTCAGCTATTAGTGGTAGTGGTAGCACATACTACGCA
35	GACTCCGTGAAGGGCCGGTTACCATCTCCAGAGACAATTCCAAGAACACGCTATATCTGC

AAATGAACAGCCTGAGAGCCGAGGACACGGCCTATATTACTGTGCGAAGTCTCTATCG
GTGGGAGCTTCTTGACTTCTGGGGCAAGGGGACAATGGTCACCGTCTCGAGT

5 FAT 7 Heavy Chain Amino Acid sequence SEQ ID NO. 24

Q	V	Q	L	V	E	S	G	G	G	L	V	Q	P	G	G	S	L	R	L	S	
C	A	A	S	G	F	T	F	S	S	Y	A	M	S	W	V	R	Q	A	P	G	
K	G	L	E	W	V	S	A	I	S	G	S	G	G	S	T	Y	Y	A	D	S	
10	V	K	G	R	F	T	I	S	R	D	N	S	K	N	T	L	Y	L	Q	M	N
	S	L	R	A	E	D	T	A	L	Y	Y	C	A	K	<u>S</u>	<u>L</u>	<u>Y</u>	<u>R</u>	<u>W</u>	<u>E</u>	<u>L</u>
	<u>L</u>	<u>D</u>	<u>F</u>	<u>W</u>	<u>G</u>	<u>K</u>	<u>G</u>	<u>T</u>	<u>M</u>	<u>V</u>	<u>T</u>	<u>V</u>	<u>S</u>	<u>S</u>							

FAT 7 Light Chain DNA sequence SEQ ID NO. 25

15	TCTTCTGAGCTGACTCAGGACCCTGCTGTGCTGTGGCCTGGGACAGACAGTCAGGATCA
	CATGCCAAGGAGACAGCCTCAGAAGCTATTATGCAAGCTGGTACCGAGCAGAACGCCAGGACA
	GGCCCCTGTACTTGTCACTATGGTAAAAACAACCGGCCCTCAGGGATCCCAGACCGATTC
	TCTGGCTCCAGCTCAGGAAACACAGCTTCCTGACCATCACTGGGCTCAGGCAGGAGATG
20	AGGCTGACTATTACTGTAACCTCCGGGACAGCAGTGGTAACCATGTGGTATTGGCGGGAGG
	GACCAAGCTGACCGTCCTAGGTGCGGCCGCACATCATCACCATCAC

FAT 7 Light Chain Amino Acid sequence SEQ ID NO. 26

25	S	S	E	L	T	Q	D	P	A	V	S	V	A	L	G	Q	T	V	R	I	T
	C	Q	G	D	S	L	R	S	Y	Y	A	S	W	Y	Q	Q	K	P	G	Q	A
	P	V	L	V	I	Y	G	K	N	N	R	P	S	G	I	P	D	R	F	S	G
	S	S	S	G	N	T	A	S	L	T	I	T	G	A	Q	A	E	D	E	A	D
	Y	Y	C	N	S	R	D	S	S	G	N	H	V	V	F	G	G	G	T	K	L
30	T	V	L	G																	

FAT 8 Heavy Chain DNA Sequence SEQ ID NO. 27

1 CAGGTGCAGCTACAGCAGTGGGGGGAGGCCTGGTCCAGCCTGGGAGGTCCCTGAGACTCT
 CCTGTGCAGCCTCTGGATTACCTCAGTAGCTATGGCATGCACGGTCCGCCAGGCTCC
 AGGCAAGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTATTAAATACTATGCA
 GACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCAGTTATCTGC
 5 AATTGACTGGCCTGAGAGCCGAGGACACGGCTGTCTATTACTGTGCAAGAGATCGGAGACT
 ACAGGATGCTTGATATCTGGGCCAAGGGACA

FAT 8 Heavy Chain Amino Acid sequence SEQ ID NO. 28

10	Q	V	Q	L	Q	Q	W	G	G	G	V	V	Q	P	G	R	S	L	R	L	S	
	C	A	A	S	G	F	T	F	S	S	Y	G	M	H	W	V	R	Q	A	P	G	
	K	G	L	E	W	V	A	V	I	S	Y	D	G	S	I	K	Y	Y	A	D	S	
	V	K	G	R	F	T	I	S	R	D	N	A	K	N	S	V	Y	L	Q	L	T	
	G	L	R	A	E	D	T	A	V	Y	Y	C	A	R	<u>D</u>	R	R	L	Q	D	A	
15	<u>F</u>	D	<u>I</u>	W	G	Q	G	T														

FAT 8 Light Chain DNA and Amino Acid sequence

Identical to FAT 1 (SEQ ID NO.'s 3 and 4)

20

FAT 9 Heavy Chain DNA Sequence SEQ ID NO. 29

GGGGTGCAGCTGGTGCATCTGGGGGAGGCCTGGTCCAGCCTGGGAGGTCCCTGAGACTCT
 CCTGTGCAGCCTCTGGATTACCTCAGTAGCTATGGCATGCACGGTCCGCCAGGCTCC
 25 AGGCAAGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTATTAAATACTATGCA
 GACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGC
 AAATGAACAGCCTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGCGAGAATTAGGATT
 TAGTGGCCCTTGATTACTGGGCCAGGGACAATGGTCACCGTCTCGAGT

30 FAT 9 Heavy Chain Amino Acid sequence SEQ ID NO. 30

	G	V	Q	L	V	Q	S	G	G	G	V	V	Q	P	G	R	S	L	R	L	S
	C	A	A	S	G	F	T	F	S	S	Y	G	M	H	W	V	R	Q	A	P	G
	K	G	L	E	W	V	A	V	I	S	Y	D	G	S	I	K	Y	Y	A	D	S
35	V	K	G	R	F	T	I	S	R	D	N	S	K	N	T	L	Y	L	Q	M	N

S	L	R	A	E	D	T	A	V	Y	Y	C	A	R	<u>E</u>	<u>L</u>	<u>G</u>	<u>F</u>	<u>S</u>	<u>G</u>	<u>P</u>
<u>F</u>	<u>D</u>	<u>Y</u>	W	G	Q	G	T	M	V	T	V	S	S							

FAT 9 Light Chain DNA and Amino Acid sequences

5

Identical to FAT 1 (SEQ ID NO.'s 3 and 4)

FAT 10 Heavy Chain DNA Sequence SEQ ID NO. 31

10 CAAGTACAGCTGCAGCAGTCAGGGCTGAGGTGAAGAAGCTGGCTCAGTGAAGGTTCTG
 CAAGGTTCTGGATACACTCACTAGTCATGCTATGCATTGGGTGCGCCAGGCCCCGGACA
 AAGGCTTGAGTGGATGGATGGATCAACGCTGGCAATGGTAAAATAAGATATTACAGAGG
 TTGCAGGGCAGAGTCACAATTACCAGGGATACATCCGCGAGCACAGCCTACATGGAGCTGA
 GAAGCCTGAGATATGAAGACACGGCTGTCTATTACTGTGCGAGATTCCGTGGATCTGGAAG
 15 TTTTGATGTCTGGGCCAAGGAACCCTGGTCACCGTCTCGAGT

FAT 10 Heavy Chain Amino Acid sequence SEQ ID NO. 32

Q	V	Q	L	Q	Q	S	G	A	E	V	K	K	L	G	S	V	K	V	S	A	
R	F	W	I	H	F	T	S	H	A	M	H	W	V	R	Q	A	P	G	Q	R	
L	E	W	M	G	W	I	N	A	G	N	G	K	I	R	Y	S	Q	R	L	Q	
25	G	R	V	T	I	T	R	D	T	S	A	S	T	A	Y	M	E	L	R	S	L
R	Y	E	D	T	A	V	Y	Y	C	A	R	<u>F</u>	<u>R</u>	<u>G</u>	<u>S</u>	<u>G</u>	<u>S</u>	<u>F</u>	<u>D</u>	<u>V</u>	
W	G	Q	G	T	L	V	T	V	S	S											

FAT 10 Light Chain DNA and Amino Acid sequences

30

Identical to FAT 7 (SEQ ID NO.'s 25 and 26)

FAT 11 Heavy Chain DNA sequence SEQ ID NO. 33

10

CAGGTGCAGCTGGTGGAGTCTGGGGAGTCGTGGTACATCCTGGCAGGTCCCTGAGACTCT
 CCTGTGCAGCCTCTGGATTACCTTGATGATTATGCCATGCACTGGGTCCGGCAAGCTCC
 AGGGAGGGGACTGGAGTGGTCTCAGGTCTTAGTGGTAGCGGTGGTAGTACATATTACGCA
 GACTCCGTGAAGGGCCGGTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGC
 5 AAATGAAAAGCCTGAGAGCCGAGGACACGCCGTCTATTACTGCGCAAAGATCTCGGCAC
 CGGGGACAGCAACTATCAGTTCTACTACATGGACGTCTGGGCCAAGGGACAATGGTCACC
 GTA

FAT 11 Heavy Chain Amino Acid sequence SEQ ID NO. 34

10 Q V Q L V E S G G V V V H P G R S L R L S
 C A A S G F T F D D Y A M H W V R Q A P G
 R G L E W V S G L S G S G G S T Y Y A D S
 V K G R F T I S R D N S K N T L Y L Q M K
 15 S L R A E D T A V Y Y C A K D L G T G D S
 N Y Q F Y Y M D V W G Q G T M V T V W L

FAT 11 Light Chain DNA Sequence SEQ ID NO. 35

20 TCGTCTGAGCTGACTCAGGACCCTGCTGTGTCTGTGGCCTGGGACAGACAGTCAGGATCA
 CATGCCAAGGAGGCAGCCCCAGAACAGCTATTATGCAAGCTGGTACCGAGCAGAACGCCAGGACA
 GGCCCCCTGTACTTGTCACTATGGTAAAAACAACCGGCCCTCAGGGATCCCAGACCGATTC
 TCTGGCTCCAGCTCAGGAAACACAGCTTCCTGACCATCACTGGGCTCAGGCAGGAAGATG
 AGGCTGACTATTACTGTCAATTCCCGGACAGCAGTGGTAACCATGTGCTTTCGGCGGAGG
 25 GACCAAGCTGACCGTCGTAGGT

FAT 11 Light Chain Amino Acid Sequence SEQ ID NO. 36

30 S S E L T Q D P A V S V A L G Q T V R I T
 C Q G G S P R S Y Y A S W Y Q Q K P G Q A
 P V L V I Y G K N N R P S G I P D R F S G
 S S S G N T A S L T I T G A Q A E D E A D
 Y Y C H S R D S S G N H V L F G G G T K L
 T

35

11

FAT 12 Heavy Chain DNA Sequence SEQ ID NO. 37

5 GAGGTGCAGCTGGTGCAGTCTAGGGCTGCGGCGAGGAAGCCGAGGGCCTCAGTGCGGGTCT
 CCTGCAAGGCTTCCGGTTACACCTCACCAATAATGCTTACATTGGGTGCGCCAGGCC
 CGGACAAAGTCTTGAGTGGATGGATGGATCAACACTGGCAATGGATCACAAAATATTCA
 CAGAGGTTTCGTGACAGAGTCACCATTACCAGGGACACATCCGCGAGCACAGTCTACATGG
 AGGTGCACAGCCTGACACCCGGAGACACGGCTGTCTATTCTGTGCGAGATGGGGAGACTT
 CTACTACTACATGGACGTCTGGGCCAAGGAACCCTGGTCACCGTCTCGAGT

10 FAT 12 Heavy Chain Amino Acid sequence SEQ ID NO. 38

E	V	Q	L	V	Q	S	R	A	A	A	R	K	P	R	A	S	V	R	V	S	
C	K	A	S	G	Y	T	F	T	N	N	A	L	H	W	V	R	Q	A	P	G	
Q	S	L	E	W	M	G	W	I	N	T	G	N	G	I	T	K	Y	S	Q	R	
15	F	R	D	R	V	T	I	T	R	D	T	S	A	S	T	V	Y	M	E	V	H
S	L	T	P	G	D	T	A	V	Y	F	C	A	R	W	G	D	F	Y	Y	Y	
<u>M</u>	<u>D</u>	<u>V</u>	<u>W</u>	<u>G</u>	<u>Q</u>	<u>G</u>	<u>T</u>	<u>L</u>	<u>V</u>	<u>T</u>	<u>V</u>	<u>S</u>	<u>S</u>								

FAT 12 Light Chain DNA Sequence SEQ ID NO. 39

20 GACATCGTGATGACCCAGTCTCCTCCACCCGTCTGCATCTGTAGGAGACAGAGTCACCA
 TCACTTGCAGGGCCAGTCAGGGTATTAGTAGCTGGTTGGCCTGGTATCAGCAGAAACCAGG
 GAGAGCCCTAAGGTCTTGATCTATAAGGCATCTACTTTAGAAAGTGGGGTCCCATCAAGG
 TTCAGCGGCAGTGGATCTGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAG
 25 ATTGCAACTTACTACTGTCAACAGAGTTACAGTAACCCGTGGACGTTGGCCAAGGAC
 CAAGCAGGAGATCAAACGT

FAT 12 Light Chain Amino Acid Sequence SEQ ID NO. 40

30	D	I	V	M	T	Q	S	P	S	T	L	S	A	S	V	G	D	R	V	T	I
T	C	R	A	S	Q	G	I	S	S	W	L	A	W	Y	Q	Q	K	P	G	R	
A	P	K	V	L	I	Y	K	A	S	T	L	E	S	G	V	P	S	R	F	S	
G	S	G	S	G	T	D	F	T	L	T	I	S	S	L	Q	P	E	D	F	A	
T	Y	Y	C	Q	Q	S	Y	S	N	P	V	D	V	R	P	R	T	K	Q	E	
35	I	K	R																		

FAT 13 Heavy Chain DNA Sequence SEQ ID NO. 41

CAGGTGCAGCTACAGCAGTGGGGCTCAGGACTGATGAAGCCCTCGGAGACCCTGTCCCTCA
 CCTGCACTGTCTCTGGTACTCTATTAACAATAATGAATATCACTGGGCCTGGATCCGCCA
 5 GCCCCCAGGGAAGGGACTGGAGTGGATTGGGTATATCAATCACAGAGGAATTGGAACCACC
 AACCAACCCCTCCCTCAAGAGTCGAGTCACCATGTCAGTAGACACGTCCAAGAACAGT
 TCTCCCTGAAGCTGAGCTCTGTGACCGCTGCGGACACGGCCGTATATTATTGTGCGAGAGA
 TAACTGGGGATCGCTGGACTACTGGGGGGACCAACGGTTACCGTATCAAGT

10 FAT 13 Heavy Chain Amino Acid sequence SEQ ID NO. 42

Q	V	Q	L	Q	Q	W	G	S	G	L	M	K	P	S	E	T	L	S	L	T	
C	T	V	S	G	D	S	I	N	N	N	E	Y	H	W	A	W	I	R	Q	P	
P	G	K	G	L	E	W	I	G	Y	I	N	H	R	G	I	G	T	T	N	H	
15	N	P	S	L	K	S	R	V	T	M	S	V	D	T	S	K	N	Q	F	S	L
K	L	S	S	V	T	A	A	D	T	A	V	Y	Y	C	A	R	D	N	W	G	
S	L	D	Y	W	G	R	G	T	T	V	T	V	S	S							

FAT 13 Light Chain DNA Sequence SEQ ID NO. 43

20 GCACCTTAATTTATGCTGACTCAGCCCCACTCTGTGTCGGAGTCTCCGGGAAGACGGTAA
 CCATCTCCTGCACCCGCAGCAGCGGCAGCATTGCCAGCAACTATGTGCAGTGGTACCAAGCA
 GCGCCCGGGCAGTCCCCCACCACACTGTGATCTATGAGGATAACCAAAGACCCCTGGGGTC
 CCTGATCGGTTCTCTGGCTCCATCGACAGCTCCTCAAACCTGCCTCCCTACCATCTTG
 25 GACTGAAGACTGAGGACGAGGCTGACTACTACTGTCACTTATGATAGCAGCAATCGGGT
 GTTCGGCGGAGGGACCAAGCTGACCGTCCTAGGT

FAT 13 Light Chain Amino Acid Sequence SEQ ID NO. 44

30	A	L	N	F	M	L	T	Q	P	H	S	V	S	E	S	P	G	K	T	V	T
I	S	C	T	R	S	S	G	S	I	A	S	N	Y	V	Q	W	Y	Q	Q	R	
P	G	S	A	P	T	T	V	I	Y	E	D	N	Q	R	P	S	G	V	P	D	
R	F	S	G	S	I	D	S	S	S	N	S	A	S	L	T	I	S	G	L	K	
T	E	D	E	A	D	Y	Y	C	Q	S	Y	D	S	S	N	R	V	F	G	G	
35	G	T	K	L	T	V	L	G													

13

FAT 14 Heavy Chain DNA Sequence SEQ ID NO. 45

5 AAGGTGCAGCTGGTGCAGTCTGGGCTGAGGTGAAGAAGCCTGGTCGTCGGTGAAGGTCA
 CCTGCGAGGCTTCCGGAGGCTACTTCAGTAGTTATGCTTCAACTGGGTGCGACAGGCC
 TGGACAAGGGCTTGAGTGGATGGGAGGAATCATCCCTTGTTGGTACACCAAACCTCGCA
 CAGAAGTTGCAAGGCAAGGTACGATTACCGCGGACGAGTCCACGAGCACAATCTACCTGG
 AGGTGAGCAACCTGACATCTGAAGACACGGCCGTCTATTCTGTGCGAGAGGTTGGGACAC
 CTGGGGCCAAGGCACCCCTGGTCACCGTATCGTCCA

10 FAT 14 Heavy Chain Amino Acid sequence SEQ ID NO. 46

K	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	S	S	V	K	V	T	
C	E	A	S	G	G	Y	F	S	S	Y	A	F	N	W	V	R	Q	A	P	G	
Q	G	L	E	W	M	G	G	I	I	P	L	F	G	T	P	N	F	A	Q	K	
15	L	Q	G	K	V	T	I	T	A	D	E	S	T	S	T	I	Y	L	E	V	S
N	L	T	S	E	D	T	A	V	Y	F	C	A	R	<u>G</u>	<u>W</u>	<u>D</u>	<u>T</u>	<u>W</u>	<u>G</u>	<u>Q</u>	
G	T	L	V	T	V	S	S														

FAT 14 Light Chain DNA and Amino Acid sequences

20 Identical to FAT 7 (SEQ ID NO.'s 25 and 26)

FAT 15 Heavy Chain DNA Sequence SEQ ID NO. 47

25 GAGGTGCAGCTACAGCAGTGGGCCAGGACTGCTGAAGCCTCGGAGACCCTGTCCCTCA
 CCTGTAGTGTCTCGTACTCCGTAAACAGGAATAGTAACACTGGGCTGGATCCGCCA
 GACCCCAGGAAAGAAGCTGGAGTGGCTGGACTATCTCTTTAGTGGAGCGCCTACTAC
 AACCCGTCCTCCAGGGTCGAGCCACCATATCGATGGACACGTCCAAGAATCAGTTGTCCC
 TGAAGCTGAGGTCTGTGACCGCTCGGACACGGCCGTCTACTACTGTGCGAGGTATAAGTG
 30 GAACACTTGGTTCGACCCCTGGGCAGAGGAACCTGGTCACCGTCTCGAGT

FAT 15 Heavy Chain Amino Acid sequence SEQ ID NO. 48

E	V	Q	L	Q	Q	W	G	P	G	L	L	K	P	S	E	T	L	S	L	T	
35	C	S	V	S	R	D	S	V	N	R	N	S	N	Y	W	G	W	I	R	Q	T

14

P	G	K	K	L	E	W	L	G	T	I	S	F	S	G	S	A	Y	Y	N	P	
S	L	Q	G	R	A	T	I	S	M	D	T	S	K	N	Q	L	S	L	K	L	
R	S	V	T	A	A	D	T	A	V	Y	Y	C	A	R	<u>Y</u>	<u>K</u>	<u>W</u>	<u>N</u>	<u>T</u>	<u>W</u>	
<u>F</u>	<u>D</u>	<u>P</u>	<u>W</u>	<u>G</u>	<u>R</u>	<u>G</u>	<u>T</u>	<u>L</u>	<u>V</u>	<u>T</u>	<u>V</u>	<u>S</u>	<u>S</u>								

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FAT 15 Light Chain DNA and Amino Acid sequences

Identical to FAT 7 (SEQ ID NO.'s 25 and 26)

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FAT 16 Heavy Chain DNA Sequence SEQ ID NO. 49

GGGGTGCAGCTGGTGCAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCT
15 CCTGTGCAGCCTCTGGATTACACCTTCTAGCAGCTATGCCATGAGCTGGTCCGCCAGGCTCC
AGGGAAGGGGCTGGAGTGGATCTCAGCTATTAGTGGTAGTGGTGGTGCCACATTCTACGCA
GACTCCGTGAAGGGCCGTTCACCATCTCCAGAGACAATTCCAAGGACACGCTGTATCTGC
AAATGAACAGCCTGAGAGCCGAGGACACGCCGTATATTACTGTGCGAAGTCTCTATCG
ATGGGAACTCTTGACTTCTGGGGCCGAGGCACCCCTGGTACCGTATCTTC

20

FAT 16 Heavy Chain Amino Acid sequence SEQ ID NO. 50

G	V	Q	L	V	Q	S	G	G	G	L	V	K	P	G	G	S	L	R	L	S	
C	A	A	S	G	F	T	F	S	S	Y	A	M	S	W	V	R	Q	A	P	G	
25	K	G	L	E	W	I	S	A	I	S	G	S	G	G	A	T	F	Y	A	D	S
V	K	G	R	F	T	I	S	R	D	N	S	K	D	T	L	Y	L	Q	M	N	
S	L	R	A	E	D	T	A	V	Y	Y	C	A	K	<u>S</u>	<u>L</u>	<u>Y</u>	<u>R</u>	<u>W</u>	<u>E</u>	<u>L</u>	
<u>F</u>	<u>D</u>	<u>F</u>	<u>W</u>	<u>G</u>	<u>R</u>	<u>G</u>	<u>T</u>	<u>L</u>	<u>V</u>	<u>T</u>	<u>V</u>	<u>S</u>	<u>S</u>								

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FAT 16 Light Chain DNA and Amino Acid sequences

Identical to FAT 7 (SEQ ID NO.'s 25 and 26)

FAT 17 Heavy Chain DNA Sequence SEQ ID NO. 51

35

CAGGTGCAGCTGGTGGAGTCTGGGGAGGCCTGGTACAGCCTGGGAGGTCCCTGAGACTCT
 CCTGTGCAGCCTCTGGATTACCTTAGCAGCTATGCCATGAGCTGGGTCCGCCAGGTCC
 AGGGAAGGGCTGGAGTGGATCTCAGCTATTAGTGCCAGTAGTGGTAGCACATATTACGCA
 GACCCCGTGAAGGGCCGATTCAACCATCTCCAGAGACAATTCCAAGAACACGCTGTTCTGC
 5 AAATGAACGGCCTGAGAGCCGAGGACACGGCCTATATTACTGTGCGAAGTCTCTCTTCG
 GTGGGAGCTATTGACCTCTGGGCCAGGGCACCGTCTCGAGT

FAT 17 Heavy Chain Amino Acid sequence SEQ ID NO. 52

10	Q	V	Q	L	V	E	S	G	G	G	L	V	Q	P	G	R	S	L	R	L	S
	C	A	A	S	G	F	T	F	S	S	Y	A	M	S	W	V	R	Q	V	P	G
	K	G	L	E	W	I	S	A	I	S	A	S	S	G	S	T	Y	Y	A	D	P
	V	K	G	R	F	T	I	S	R	D	N	S	K	N	T	L	F	L	Q	M	N
	G	L	R	A	E	D	T	A	L	Y	Y	C	A	K	<u>S</u>	<u>L</u>	<u>F</u>	<u>R</u>	<u>W</u>	<u>E</u>	<u>L</u>
15	<u>F</u>	<u>D</u>	<u>L</u>	W	G	Q	G	T	L	V	T	V	S	S							

FAT 17 Light Chain DNA Sequence SEQ ID NO. 53

TCGTCTGAGCTGACTCAGGACCCTGCTGTGTCTGGCCTTGGACAGACAGTCAGGATCA
 20 CATGCCAAGGAGACAGCCTCAGAACAGCTATTATGCAAGCTGGTACCAGCAGAACCCAGGACA
 GGCCCTGTACTTGTATCTATGGTAAAACAAGCAGCCCTCAGGGATCCCAGACCGATTCT
 TCTGGCTCCAGCTCAGGAAACACAGCTTCCTTGACCATCACTGGGCTCAGGCAGGAGATG
 AGGCTGACTATTACTGTCAATTCCCGGGACAGCAGTGGTAACCATGTGCTTTGGCGGAGG
 GACCAAGCTGACCGTCCTAGGT

25

FAT 17 Light Chain Amino Acid Sequence 54

	S	S	E	L	T	Q	D	P	A	V	S	V	A	L	G	Q	T	V	R	I	T
	C	Q	G	D	S	L	R	S	Y	Y	A	S	W	Y	Q	Q	K	P	G	Q	A
30	P	V	L	V	I	Y	G	K	N	K	R	P	S	G	I	P	D	R	F	S	G
	S	S	S	G	N	T	A	S	L	T	I	T	G	A	Q	A	E	D	E	A	D
	Y	Y	C	H	S	R	D	S	S	G	N	H	V	L	F	G	G	G	T	K	L
	T	V	L	G																	

35 FAT 18 Heavy Chain DNA Sequence SEQ ID NO. 55

CAGGTGCAGCTACAGCAGTGGGCCAGGACTGGTGAAGCCCTCGGAGACCCTGTCACTCA
 CGTGCTCTGTCTGGTGGCTCCCTCGATGACTTCTCTGGAGCTGGATCCGGCAGTCCCC
 AGGGAAGGGCCTGGAGTGGTCGCGAGTATCGGCCACTGGCAACATACACAGTTCTCCC
 TCCCTCAGGAGGCAGTCACCATGTCAACAGACACGTCCAGAAATCAGTTCTCCCTCAATT
 5 TGACTTCTGTGACCGCTGCGGACACGGCCGTCTATTACTGTGCGAGAGATGGGAGAGCCC
 ACTGGACTTTACTTCGATTCTGGGCCGAGGAACCCTGGTCACCGTCTCGTCC

FAT 18 Heavy Chain Amino Acid sequence SEQ ID NO. 56

10	Q	V	Q	L	Q	Q	W	G	P	G	L	V	K	P	S	E	T	L	S	L	T	
	C	S	V	S	G	G	S	L	D	D	F	F	W	S	W	I	R	Q	S	P	G	
	K	G	L	E	W	V	A	S	I	G	A	T	G	N	I	H	S	S	P	S	L	
	R	R	R	V	T	M	S	T	D	T	S	R	N	Q	F	S	L	N	L	T	S	
	V	T	A	A	D	T	A	V	Y	Y	C	A	R	<u>D</u>	<u>G</u>	<u>E</u>	<u>S</u>	<u>P</u>	<u>L</u>	<u>D</u>	<u>F</u>	
15	<u>Y</u>	<u>F</u>	<u>D</u>	<u>F</u>	W	G	R	G	T	L	V	T	V	S	S							

FAT 18 Light Chain DNA and Amino Acid sequences

Identical to FAT 7 (SEQ ID NO.'s 25 and 26)

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FAT 19 Heavy Chain DNA Sequence SEQ ID NO. 57

25 CAGATGCAGCTGGTGCAGTTGGGGAGGCAGTGGTCCAGCCTGGAGGTCCCTGAGACTTT
 CCTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCAGTGGTCCGCCAGGCTCC
 AGGCAAGGGCTGGAGTGGTGGCAGTTATATCATATGATGGAAGTATTAAATACTATGCA
 GACTCCGTGAAGGGCCGATTACCACATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGC
 30 AAATGAACAGCCTGAGAGCTGACGACACGGCTGTCTATTACTGTGCGAGAGACAGTTGGAT
 AAGCGGAAACTTGACTACTGGGCCAAAGGGACAATTGTGCACAGT

FAT 19 Heavy Chain Amino Acid sequence SEQ ID NO. 58

17

Q	M	Q	L	V	Q	F	G	G	G	V	V	Q	P	G	R	S	L	R	L	S	
C	A	A	S	G	F	T	F	S	S	Y	G	M	H	W	V	R	Q	A	P	G	
K	G	L	E	W	V	A	V	I	S	Y	D	G	S	I	K	Y	Y	A	D	S	
V	K	G	R	F	T	I	S	R	D	N	S	K	N	T	L	Y	L	Q	M	N	
5	S	L	R	A	D	D	T	A	V	Y	Y	C	A	R	<u>D</u>	<u>S</u>	<u>W</u>	<u>I</u>	<u>S</u>	<u>G</u>	<u>N</u>
	<u>F</u>	<u>D</u>	<u>Y</u>	<u>W</u>	<u>G</u>	<u>K</u>	<u>G</u>	<u>T</u>													

FAT 19 Light Chain DNA and Amino Acid sequences

10 Identical to FAT 1 (SEQ ID NO.'s 3 and 4)

FAT 20 Heavy Chain DNA Sequence SEQ ID NO. 59

GAGGTGCAGCTGGTGGAGTTGGGGGAGGCTTGGTACAGCCGGGGGGTCCCTGAGACTCT
 15 CCTGTGCAGGCTCTGGATTCAAGTTTAGTCGCTATGCCATAAGCTGGTCCGCCAGGCTCC
 AGGGAAGGGGCTGGAGTGGGTCTCAGCTATTGGTGAAGCGGTGTTAGCACATTACGCA
 GGCTCCGTGAGGGGCCGGTCTCCATCTCAGAGACAATTCCAAGAACACACTGTATCTGC
 AAATGAACAGCCTGAGAGCTGAGGACACGGCTGTATTACTGTGCGAGAGATTATTCGA
 TATTCTGACTGGTCCATGGACGTCTGGGGCCGAGGCACCCCTGTCACA

20

FAT 20 Heavy Chain Amino Acid sequence SEQ ID NO. 60

E	V	Q	L	V	E	F	G	G	G	L	V	Q	P	G	G	S	L	R	L	S	
C	A	G	S	G	F	S	F	S	R	Y	A	I	S	W	V	R	Q	A	P	G	
25	K	G	L	E	W	V	S	A	I	G	G	S	G	V	S	T	F	Y	A	G	S
V	R	G	R	F	S	I	S	R	D	N	S	K	N	T	L	Y	L	Q	M	N	
S	L	R	A	E	D	T	A	V	Y	Y	C	A	R	<u>D</u>	<u>Y</u>	<u>F</u>	<u>D</u>	<u>I</u>	<u>L</u>	<u>T</u>	
	<u>G</u>	<u>P</u>	<u>M</u>	<u>D</u>	<u>V</u>	<u>W</u>	<u>G</u>	<u>R</u>	<u>G</u>	<u>T</u>	<u>L</u>	<u>V</u>	<u>T</u>								

30 FAT 20 Light Chain DNA Sequence SEQ ID NO. 61

TCGTCTGAGCTGACTCAGGACCCCTGCTGTGCTGTGGCCTGGGACAGACAGTCAGGATCA
 CATGCCAAGGAGACAGCCTCAGAACAGCTATTATGCAAGCTGGTACCGAGCAGGCCAGGGCA
 GGCCCTGTACTGTCATCTATGGTAAAACAACCGGCCCTCAGGGATCCCAGACCGATTC
 35 TCTGGCTCCAGCTCAGGAAACACAGCTTCCTGACCATCACTGGGCTCAGGCGGAAGATG

AGGCTGACTATTACTGTCATTCCCGGGACAGCAGTGGTAACCATGTGCTTCGGCGGAGG
GACCAAGCTGACC

FAT 20 Light Chain Amino Acid Sequence SEQ ID NO. 62

5

FAT 21 Heavy Chain DNA Sequence SEQ ID NO. 63

15 GAGGTGCAGCTGGTGCAGTCTGGGGAGGCAGGTCCAGCCTGGGGGTCCCTGAGAGTCT
CCTGTGCAGCCTCTGGCTCCCTCAGTCACTATGCCATGCACTGGTCCGCCAGGCC
AGGCAAGGGCTGGAGTGGTTCATACATTAGTGAAGTGAAGTTATACAGGGTACGCA
GACTCTGTGAAGGGCCGATTCAACCCTCAGAGACAACGCCAAGAATTCACTGTATCTGC
AAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGAGGTCACTA
20 CTACGGTATGGATGTCTGGGCAAGGGCACCATTGTCACAGTG

FAT 21 Heavy Chain Amino Acid sequence SEQ ID NO. 64

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FAT 21 Light Chain DNA and Amino Acid sequences

Identical to FAT 7 (SEQ ID NO.'s 25 and 26)

FAT 22 Heavy Chain DNA Sequence SEQ ID NO. 65

CAGGTGCAGCTGGTCAATCTGGGGAGGCCTGGTCCAGCCTGGGAGGTCCCTGAGACTCT
 5 CCTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACGGTCCGCCAGGCTCC
 AGGCAAGGGGCTGGAGTGGGTGGCAGTCGTCTGGCATGATGGCAGTAATGAGTATTATGCA
 GACTCCGTGAAGGGCCGATTCAACCCTCCAGAGACAACCTCAAGAACAGCCTATTCTGC
 AAATGAACAAACCTGAGCTCCGAGGATAACGGCTGTCTATTACTGTGCGAGGGGGTGGTGGTC
 GACCAACACCTACTATTTGACTATTGGGCAAGGAACCTGGTACCGTCTCGAGT

10

FAT 22 Heavy Chain Amino Acid sequence SEQ ID NO. 66

Q	V	Q	L	V	Q	S	G	G	G	V	V	Q	P	G	R	S	L	R	L	S	
C	A	A	S	G	F	T	F	S	S	Y	G	M	H	W	V	R	Q	A	P	G	
15	K	G	L	E	W	V	A	V	V	W	H	D	G	S	N	E	Y	Y	A	D	S
V	K	G	R	F	T	I	S	R	D	N	S	K	N	S	L	F	L	Q	M	N	
N	L	S	S	E	D	T	A	V	Y	Y	C	A	R	<u>G</u>	<u>W</u>	<u>W</u>	<u>S</u>	<u>T</u>	<u>N</u>	<u>T</u>	
<u>Y</u>	<u>Y</u>	<u>F</u>	<u>D</u>	<u>Y</u>	<u>W</u>	<u>G</u>	<u>K</u>	<u>G</u>	<u>T</u>	<u>L</u>	<u>V</u>	<u>T</u>	<u>V</u>	<u>S</u>	<u>S</u>						

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FAT 22 Light Chain DNA Sequence SEQ ID NO. 67

GACATCCAGTTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCA
 TCACTGCCAGCGAGTCAGGACATTAGCAACTATTAAATTGGTATCAGCAGAAACCAGG
 GAAAGCCCCTAACGCTCCTGATCTACGATGCATCCAATTGGAACAGGGGTCCCATCAAGG
 25 TTCAGTGGAAAGTGGATCTGGGACAGATTACTTACCATCAGCAGCCTGCAGCCTGAAG
 ATATTGCAACATATTACTGTCAACAGTATGATAATCTCCGATCACCTCGGCCAAGGGAC
 ACGACTGGAGATTAAACGT

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FAT 22 Light Chain Amino Acid Sequence SEQ ID NO. 68

D	I	Q	L	T	Q	S	P	S	S	L	S	A	S	V	G	D	R	V	T	I	
T	C	Q	A	S	Q	D	I	S	N	Y	L	N	W	Y	Q	Q	K	P	G	K	
A	P	K	L	L	I	Y	D	A	S	N	L	E	T	G	V	P	S	R	F	S	
35	G	S	G	S	G	T	D	F	T	F	T	I	S	S	L	Q	P	E	D	I	A

20

T	Y	Y	C	Q	Q	Y	D	N	L	P	I	T	F	G	Q	G	T	R	L	E
I	K	R																		

FAT 23 Heavy Chain DNA Sequence SEQ ID NO. 69

5 CAGGTGCAGCTGCAGGAGTCGGGGCTGAGGTGAAGAAGTCTGGGCTTCAGTGAAGGTTT
 CCTGCAAGGCATCTGGATACTTCACCAAGCTACTATGCACCTGGGTGCGACAGGCC
 TGGACAAGGGCTTGAGTGGATGGAAATAATCAACCTAGTGGTGGTAGCACAAGCTACGCG
 CAGAAGTTCCAGGGCAGAGTCACCATGACCAGGGACACGTCCACGAGCACAGTCTACATGG
 10 AGCTGAGCAGCCTGAGATCTGAGGACACGCCGTGTATTACTGTGCGAGAGATAGTGGCTA
 CGATGGCACGGTATGGACGTCTGGGCCAGGAACCTGGTCACCGTCTCGAGT

FAT 23 Heavy Chain Amino Acid sequence SEQ ID NO. 70

15	Q	V	Q	L	Q	E	S	G	A	E	V	K	K	S	G	A	S	V	K	V	S	
	C	K	A	S	G	Y	T	F	T	S	Y	Y	M	H	W	V	R	Q	A	P	G	
	Q	G	L	E	W	M	G	I	I	N	P	S	G	G	S	T	S	Y	A	Q	K	
	F	Q	G	R	V	T	M	T	R	D	T	S	T	S	T	V	Y	M	E	L	S	
	S	L	R	S	E	D	T	A	V	Y	Y	C	A	R	<u>D</u>	S	G	Y	D	G	H	
20	<u>G</u>	<u>M</u>	<u>D</u>	<u>V</u>	<u>W</u>	<u>G</u>	<u>R</u>	<u>G</u>	<u>T</u>	<u>L</u>	<u>V</u>	<u>T</u>	<u>V</u>	<u>S</u>	<u>S</u>							

FAT 23 Light Chain DNA and Amino Acid sequences

25 Identical to FAT 7 (SEQ ID NO.'s 25 and 26)

FAT 25 Heavy Chain DNA sequence SEQ ID NO. 71

30 GAGGTGCAGCTGGTGGAGTCTGGGGAGGCGTGGTCCAGCCTGGAGGTCCCTGAGACTCT
 CCTGTGCAGCCTCTGGATTACCTTCAGGAACATGGCATGCACCTGGTCCGCCAGGCTCC
 AGGCAAGGGCTGGAGTGGGTGGCAGTGATATCATATGATGGAAGTAATAAAACTATGCA
 GACTCCGTGGAGGGCCGATTACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGC
 AAATGAACAGCCTGAGAGTCGAGGACACGGCTGTTATTACTGTGCGAGAAGATGGTATGG
 TGGCAGTGGTTATTGGGCCACTTCTACTCCTACATGGACGGCTGGGCAAAGGGACCAAG
 35 GTCACCGTCTCCTCA

FAT 25 Heavy Chain Amino Acid sequence SEQ ID NO. 72

	E	V	Q	L	V	E	S	G	G	V	V	Q	P	G	R	S	L	R	L	S	
5	C	A	A	S	G	F	T	F	R	N	Y	G	M	H	W	V	R	Q	A	P	G
	G	L	E	W	V	A	V	I	S	Y	D	G	S	N	K	Y	Y	A	D	S	V
	E	G	R	F	T	I	S	R	D	N	S	K	N	T	L	Y	L	Q	M	N	S
	L	R	V	E	D	T	A	V	Y	Y	C	A	R	<u>R</u>	W	Y	G	G	S	G	Y
	W	G	H	F	Y	S	Y	M	D	G	W	G	K	G	T	K	V	T	V	S	S

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FAT 25 Light Chain DNA and Amino Acid sequences

Identical to FAT 7 (SEQ ID NO.'s 25 and 26)

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FAT 26 Heavy Chain DNA sequence SEQ ID NO. 73

GAGGTGCAGCTGGTGGAGTCTGGGGAGGCAGGTCCAGCCTGGGAGGTCCCTGAGACTCT
 CCTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGCTATGCACCTGGGTCCGCCAGGCTCC
 20 AGGCAAGGGCTGGAGTGGGTGGCAGTTATCATATGATGGAAGCAATAATACTACGCA
 GACTCCGTGAAGGCCGATTCAACCACCTCCAGAGACAATTCCAAGAACACGCTGTATCTGC
 AAATGAACAGCCTGAGAGCTGAGGACACGCCGTATTACTGTGCAAGATATTATATTC
 GGGGTGGGCCAAGGTACCTGGTCACCGTGTGCG

FAT 26 Heavy Chain Amino Acid sequence SEQ ID NO. 74

	E	V	Q	L	V	E	S	G	G	V	V	Q	P	G	R	S	L	R	L	S	
	C	A	A	S	G	F	T	F	S	S	Y	A	M	H	W	V	R	Q	A	P	G
	K	G	L	E	W	V	A	V	I	S	Y	D	G	S	N	K	Y	Y	A	D	S
30	V	K	G	R	F	T	I	S	R	D	N	S	K	N	T	L	Y	L	Q	M	N
	S	L	R	A	E	D	T	A	V	Y	Y	C	A	R	<u>Y</u>	<u>Y</u>	<u>I</u>	<u>S</u>	<u>G</u>	<u>W</u>	<u>G</u>
	Q	G	T	L	V	T	V	S													

35

Identical to FAT 2 (SEQ ID NO.'s 7 and 8)

FAT 27 Heavy Chain DNA sequence SEQ ID NO. 75

5 GAGGTGCAGCTGGTGGAGTCTGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCT
 CCTGTGCAGCCTCTGGATTCACTTCAGTAGCTATGCTATGCACTGGGTCCGCCAGGCTCC
 AGGCAAGGGGCTGGAGTGGGTGGCAGTTATCATATGATGGAAGCAATAAATACTACGCA
 GACTCCGTGAAGGGCCGATTCAACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGC
 AAATGAACAGCCTGAGAGCTGAGGACACGCCGTGTATTACTGTGCAAGATATTATGTGTC
 10 TGGGTGGGGCCAAGGTACCCCTGGTCACCGTGTGCG

FAT 27 Heavy Chain Amino Acid sequence SEQ ID NO. 76

E	V	Q	L	V	E	S	G	G	V	V	Q	P	G	R	S	L	R	L	S		
15	C	A	A	S	G	F	T	F	S	S	Y	A	M	H	W	V	R	Q	A	P	G
	K	G	L	E	W	V	A	V	I	S	Y	D	G	S	N	K	Y	Y	A	D	S
	V	K	G	R	F	T	I	S	R	D	N	S	K	N	T	L	Y	L	Q	M	N
	S	L	R	A	E	D	T	A	V	Y	Y	C	A	R	<u>Y</u>	<u>Y</u>	V	<u>S</u>	G	W	G
20	Q	G	T	L	V	T	V	S													

FAT 27 Light Chain DNA and Amino Acid sequences

Identical to FAT 2 (SEQ ID NO.'s 7 and 8)

25

FAT 28 Heavy Chain DNA Sequence SEQ ID NO. 77

30 GAGGTGCAGCTGGTGGAGTCTGGGGAGGCTTGGTAAAGCCTGGGAGTCCTTAGACTCT
 CCTGTGCAGCCTCTGGATTCACTTCAGTAACGCCTGGATGAGCTGGGTCCGCCAGGCTCC
 AGGGAAAGGGGCTGGAGTGGGTGGCCGTATTAAAAGCAAAACTGATGGTGGGACAACAGAC
 TACGCTGCACCCGTGAAAGGCAGATTCAACCATCTCAAGAGATGATTCAAAAAACACGCTGT
 ATCTGCAAATGAACAGCCTGAAACCGAGGACACGCCGTGTATTACTGTGCAAGATGGGG
 TCCTCCGGTGTATGCTAACGCTTGGGGCCAAGGTACCCCTGGTCACCGTGTGCG

35

FAT 28 Heavy Chain Amino Acid sequence SEQ ID NO. 78

E	V	Q	L	V	E	S	G	G	G	L	V	K	P	G	E	S	L	R	L	S	
C	A	A	S	G	F	T	F	S	N	A	W	M	S	W	V	R	Q	A	P	G	
5	K	G	L	E	W	V	G	R	I	K	S	K	T	D	G	G	T	T	D	Y	A
A	P	V	K	G	R	F	T	I	S	R	D	D	S	K	N	T	L	Y	L	Q	
M	N	S	L	K	T	E	D	T	A	V	Y	Y	C	A	R	W	G	P	P	V	
Y	A	K	P	W	G	Q	G	T	L	V	T	V	S								

10

FAT 28 Light Chain DNA and Amino Acid sequences

Identical to FAT 7 (SEQ ID NO.'s 25 and 26)

15 FAT 29 Heavy Chain DNA Sequence SEQ ID NO. 79

CAGGTGCAGCTGCAGGAGTCGGGCCAGGACTGGTGAAGCCTTCGGAGACCCTGTCCCTCA
 CCTGCGCTGTCTGGTTACTCCATCAGCAGTGGTTACTACTGGGGCTGGATCCGGCAGCC
 CCCAGGGAAGGGGCTGGAGTGGATTGGAGTATCTATCATAGTGGAGCACCTACTACAAAC
 20 CCGTCCCTCAAGAGTCGAGTCACCATATCAGTAGACACGTCCAAGAACAGTTCTCCCTGA
 AGCTGAGCTCTGTGACCGCCGCAGACACGGCTGTGTATTACTGTGCAAGAGTGAATAGGTA
 TGGTTCTCCTTAGACGTGGGCCAAGGTACCCCTGGTCACCGTGTGCG

FAT 29 Heavy Chain Amino Acid sequence SEQ ID NO. 80

25	Q	V	Q	L	Q	E	S	G	P	G	L	V	K	P	S	E	T	L	S	L	T
C	A	V	S	G	Y	S	I	S	S	G	Y	Y	W	G	W	I	R	Q	P	P	
G	K	G	L	E	W	I	G	S	I	Y	H	S	G	S	T	Y	Y	N	P	S	
L	K	S	R	V	T	I	S	V	D	T	S	K	N	Q	F	S	L	K	L	S	
30	S	V	T	A	A	D	T	A	V	Y	Y	C	A	R	V	N	R	Y	G	S	P
	<u>B</u>	T	W	G	Q	G	T	L	V	T	V	S									

FAT 29 Light Chain DNA and Amino Acid sequences

35 Identical to FAT 7 (SEQ ID NO.'s 25 and 26)

FAT 30 Heavy Chain DNA sequence SEQ ID NO. 81

5 GAGGTGCAGCTGGTGGAGACCGGAGCAGAGGTGAAAAAGCCGGCGAGTCTCTGAAGATT
 CCTGTGAGATTCTGGGTACACCTTACCGACTACTGGATCGCCTGGTGCGCCAGATGCC
 CGGGAAAGGCTTGGAGTGGATGGTATTATCTATCCTGGTACTCGGATGCCAGATACAGC
 CCGTCCTCGAAGGCCAGGTACCATGTCAGCCGACGAGTCCCTCAGCACCGTCTACCTCC
 AATGGAGCAGCCTGAAGCCCTCGGACAGGCCATGTATTCCTGTGCGGGCCCCATTACCC
 CATGACTACGGATGATGCTTTGATATTGGGCAAAGGAACCCTGGTCACCGTCTCGAGT

10 FAT 30 Heavy Chain Amino Acid sequence SEQ ID NO. 82

E	V	Q	L	V	E	T	G	A	E	V	K	K	P	G	E	S	L	K	I	S	
C	E	I	S	G	Y	T	F	T	D	Y	W	I	A	W	V	R	Q	M	P	G	
K	G	L	E	W	M	G	I	I	Y	P	G	D	S	D	A	R	Y	S	P	S	
15	F	E	G	Q	V	T	M	S	A	D	E	S	L	S	T	V	Y	L	Q	W	S
S	L	K	P	S	D	S	A	M	Y	F	C	A	R	P	H	Y	P	M	T	T	
D	D	A	F	D	I	W	G	K	G	T	L	V	T	V	S	S					

20

FAT 30 Light Chain DNA sequence SEQ ID NO. 83

25 CAGTCTGTGTTGACGCAGCCGCCCTCAGTGTCTGCGGCCAGGACAGAAGGTACCCATT
 CCTGCTCTGGAAGCACCTCCAACATTGGAAATAATTATGTCTCCTGGTACCAACAGCACCC
 AGGCAAAGCCCCAAACTCATGATTATGATGTCAGTAAGCGGCCCTCAGGGGTCCCTGAC
 CGATTCTCTGGCTCCAAGTCTGGCAACTCAGCCTCCCTGGACATCAGTGGCTCCAGTCTG
 AGGATGAGGCTGATTATTACTGTGCAGCATGGATGACAGCCTGAGTGAATT CCTCTTCGG
 AACTGGGACCAAGCTGACCGTCCTAGGTGCGGCCGCACATCATCACCATCAC

30 FAT 30 Light Chain Amino Acid sequence SEQ ID NO. 84

Q	S	V	L	T	Q	P	P	S	V	S	A	A	P	G	Q	K	V	T	I	S
C	S	G	S	T	S	N	I	G	N	N	Y	V	S	W	Y	Q	Q	H	P	G
K	A	P	K	L	M	I	Y	D	V	S	K	R	P	S	G	V	P	D	R	F
35	S	G	S	K	S	G	N	S	A	S	L	D	I	S	G	L	Q	S	E	E

25

A	D	Y	Y	C	A	A	W	D	D	S	L	S	E	F	L	F	G	T	G	T
K	L	T	V	L	G															

FAT 31 Heavy Chain DNA Sequence SEQ ID NO. 85

5 GAGGTGCAGCTGGTGGAGTCTGGGGGGGCTTGGTACAGCCTGGCAGGTCCCTGAGACTCT
 CCTGTGGAGGCTCTGGATTCAAGTTGATGAATATGCCATGCACGGTCCGCCAAGCTCC
 AGGCAAGGGCCTGGAGTGGGTCCCAGGTATTAATTGGAATGGTGTAGTTGGCCTATGCG
 GACTCTGTGAAGGGCCGGTTACCATCTCCAGAGACAACGCCAAGAACTCCCTGCATCTGC
 10 AAATGAACAGTTGGGACTGAGGACACGGCCTCTATTACTGTGCAAAAGCTGCCATAGC
 CTCCTTAGGCAATTGTACGAGTGCCAGTTGCTATAACGGTGCTTTGACATCTGGGCCGG
 GGGACAATGGTCACCGTC

FAT 31 Heavy Chain Amino Acid sequence SEQ ID NO. 86

15 E V Q L V E S G G G L V Q P G R S L R L S
 C G G S G F S F D E Y A M H W V R Q A P G
 K G L E W V P G I N W N G V S L A Y A D S
 V K G R F T I S R D N A K N S L H L Q M N
 20 S L G T E D T A F Y Y C A K A A I A S L G
N C T S A S C Y N G A F D I W G R G T M V
 T V

FAT 31 Light Chain DNA Sequence SEQ ID NO. 87

25 CAGTCTGTGTTGACGCAGCCGCCCTCAGTGTCTGCGGCCAGGACAGAAGGTACCCATT
 CCTGCTCTGGAAGCACCTCAACATTGGGATAATTATGTCCTGGTACCAACAGCACCC
 AGGCAAAGCCCACAAACTCATGATTATGATGTCAGTAAGCGGCCCTCAGGGGTCCCTGAC
 CGATTCTCTGGCTCCAAGTCTGGCAACTCAGCCTCCCTGGACATCAGTGGGCTCCAGTCTG
 30 AGGATGAGGCTGATTATTACTGTGCAGCATGGATGACAGCCTGAGTGAATTCTCTTCGG
 AACTGGGACCAAGCTGACCGTC

FAT 31 Light Chain Amino Acid Sequence SEQ ID NO. 88

Q	S	V	L	T	Q	P	P	S	V	S	A	A	P	G	Q	K	V	T	I	S	
C	S	G	S	T	S	N	I	G	N	N	Y	V	S	W	Y	Q	Q	H	P	G	
K	A	H	K	L	M	I	Y	D	V	S	K	R	P	S	G	V	P	D	R	F	
S	G	S	K	S	G	N	S	A	S	L	D	I	S	G	L	Q	S	E	D	E	
5	A	D	Y	Y	C	A	A	W	D	D	S	L	S	E	F	L	F	G	T	G	T
	K	L	T	V																	

FAT 32 Heavy Chain DNA sequence SEQ ID NO. 89

10 GAAGTGCAGCTGGTGCAGTTGGAGCAGGAGGTGAAAAAGCCGGGGAGTTGGAAGATCT
 CCTGTAAGGTTCTGGATACAGCTTAAACCCCAATGGCTCGGCTGGGTGCGCCAGATGCC
 CGGGAAAGGCCTGGAGTGATGGGAATCATCTATCCTGGTACTCTGATACCAAATACAGC
 CCGTCCTCCAAGGCCAGGTACCCCTCTCAGCCGACAAGTCCATCAGCACCGCCTACCTGC
 AGTGGAGCAGCCTGAAGGCCTGGACACGCCATGTATTACTATACCAGCACAGACGATGG
 15 CTACAATTTGCTTTGATATCTGGGGCAGAGGAACCCTGGTCACCGTCTCGAGT

FAT 32 Heavy Chain Amino Acid sequence SEQ ID NO. 90

E	V	Q	L	V	Q	L	E	Q	E	V	K	K	P	G	G	V	W	K	I	S	
20	C	K	G	S	G	Y	S	F	K	P	Q	W	L	G	W	V	R	Q	M	P	G
	K	G	L	E	C	M	G	I	I	Y	P	G	D	S	D	T	K	Y	S	P	S
	F	Q	G	Q	V	T	L	S	A	D	K	S	I	S	T	A	Y	L	Q	W	S
	S	L	K	A	S	D	T	A	M	Y	Y	T	S	T	D	D	G	Y	N	F	
25	A	F	D	I	W	G	R	G	T	L	V	T	V	S	S						

FAT 32 Light Chain DNA and Amino Acid sequences

Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

30 FAT 33 Heavy Chain DNA sequence SEQ ID NO. 91

CAGGTACCTTGAAGGAGTCTGGGGAGACTTGGTCAGGCCTGGAGGGTCCCTGAGACTCT
 CCTGTGCAGCCTCTGGATTACCTTCAGTGACTACTACATGACCTGGATCCGCCAGGCTCC
 AGGGAAGGGCTGGAGTGGGTTTCATACATTACTAATAGTGGTAATACCATAGACTACGCA
 35 GACTCTGTGCAGGGCCGATTCAACCATCTCCAGGGACAACGCCAAGAACTCACTGTATCTCC

27

AAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGACTGGTTCCGGGGA
 CCTTGACCACTGGGCCAGGGCACCCCTGGTCACCGTCTCGAGT

FAT 33 Heavy Chain Amino Acid sequence SEQ ID NO. 92

5

Q	V	T	L	K	E	S	G	G	D	L	V	R	P	G	G	S	L	R	L	S	
C	A	A	S	G	F	T	F	S	D	Y	Y	M	T	W	I	R	Q	A	P	G	
K	G	L	E	W	V	S	Y	I	T	N	S	G	N	T	I	D	Y	A	D	S	
V	Q	G	R	F	T	I	S	R	D	N	A	K	N	S	L	Y	L	Q	M	N	
10	S	L	R	A	E	D	T	A	V	Y	Y	C	A	T	<u>G</u>	<u>S</u>	<u>G</u>	<u>D</u>	<u>L</u>	<u>D</u>	H
	W	G	Q	G	T	L	V	T	V	S	S										

FAT 33 Light Chain DNA and Amino Acid sequences

15 Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

FAT 34 Heavy Chain DNA sequence SEQ ID NO. 93

20

GAGGTGCAGCTGGTGCAGTCTGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCT
 CCTGTGCAGCCTCTGGATTCACCTTCAGTGACTATTACATGAGCTGGATCCGCCAGACTCC
 AGGGAAGGGTCTGGAATGGATTTCATACATTAGTGATAACGGTAAACCCATATACTACGGA
 GACTCTGTGGAGGGCCGATTACCACATCTCCAGGGACAACGCCAACCGCTCACCGGATCTGC
 AAATGAACAGCCTGAGAGCCGACGACACGCCGTGTATTCTGTGCGAGAACATGGCAC
 TGGCTGGTATGTTAGCTACCTGACTTCTGGGCAAAGGCACCACGGTCACCGTCTCCTCA

25

FAT 34 Heavy Chain Amino Acid sequence SEQ ID NO. 94

30

E	V	Q	L	V	Q	S	G	G	G	L	V	K	P	G	G	S	L	R	L	S
C	A	A	S	G	F	T	F	S	D	Y	Y	M	S	W	I	R	Q	T	P	G
K	G	L	E	W	I	S	Y	I	S	D	N	G	K	T	I	Y	Y	G	D	S
V	E	G	R	F	T	I	S	R	D	N	A	N	R	S	P	D	L	Q	M	N

28

S	L	R	A	D	D	T	A	V	Y	F	C	A	R	<u>S</u>	<u>M</u>	<u>G</u>	<u>T</u>	<u>G</u>	<u>W</u>	<u>Y</u>
V	S	Y	P	D	F	W	G	K	G	T	T	V	T	V	S	S				

FAT 34 Light Chain DNA and Amino Acid sequences

5

Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

FAT 35 Heavy Chain DNA Sequence SEQ ID NO. 95

10 CAGGTCACCTTGAAGGAGTCTGGGGAGGCTTGGTCAAGGCTGGGGTTCCCTGAGACTCT
 CCTGTGCAGCCTCTGGATTCACCTTCAGTGACTACTATATGAGCTGGATCCGCCAGGCTCC
 AGGGAAGGGCTGGAGTGGATTGGGAAATCAATCAGAGTGGAACCGCCAATTACAACCCC
 TCCCTCAAGAGTCGAGTCACCTTGTCACTGGACAGGTCCCGAACCGAGTTCTCGCTGAAGC
 TGACCTCTGTGACCGCCGGACACGGCCGTGTATTATTGTGCAAGAGATAACGGTCGGGA
 15 CTATGATAGTGGTGGCTATTACTACTCTGACTCCTGGGCAAAGGCACCCGGTCACCGTC
 TCCTCA

FAT 35 Heavy Chain Amino Acid sequence SEQ ID NO. 96

20 Q V T L K E S G G G L V K A G G S L R L S
 C A A S G F T F S D Y Y M S W I R Q A P G
 K G L E W I G E I N Q S G T A N Y N P S L
 K S R V T L S V D R S A N Q F S L K L T S
 V T A A D T A V Y Y C A R D T V G D Y D S
 25 G G Y Y Y S D S W G K G T P V T V S S

FAT 35 Light Chain DNA and Amino Acid sequences

30

Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

GAGGTGCAGCTGGTGGAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTCT
 CCTGCAAGGCTTCTGGTTACACCTTACCGCTATGGTATCAGCTGGGTGCGACAGGCC
 35 TGGACAAGGGCTTGAGTGGATGGATGGATCAGCGCTTACAATGGTAACACAAACTACGCA

TAGAAGCTCCAGGGCAGAGTCACCATGACCACAGACACATCCACGAGCACAGCCTACATGG
 AGCTGAGGAGCCTGAGATCTGACGACACGGCCGTGTATTACTGTGCGAGAGATGGGTTCT
 AGACTACTACTATGGTATGGACGTCTGGGGCCGGGAACCCTGGTCACCGTCTCGAGTGGT
 GGAGGCGGTT

5

FAT 36 Heavy Chain Amino Acid sequence SEQ ID NO. 98

E	V	Q	L	V	E	S	G	A	E	V	K	K	P	G	A	S	V	K	V	S	
C	K	A	S	G	Y	T	F	T	S	Y	G	I	S	W	V	R	Q	A	P	G	
10	Q	G	L	E	W	M	G	W	I	S	A	Y	N	G	N	T	N	Y	A	B	K
L	Q	G	R	V	T	M	T	T	D	T	S	T	S	T	A	Y	M	E	L	R	
S	L	R	S	D	D	T	A	V	Y	Y	C	A	R	D	G	V	L	D	Y	Y	
Y	G	M	D	V	W	G	R	G	T	L	V	T	V	S	S						

15

FAT 36 Light Chain DNA and Amino Acid sequence

Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

20 FAT 37 Heavy Chain DNA Sequence SEQ ID NO. 99

CAGGTCCAGCTGGAGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCTCGGTGAAGGTCT
 CCTGCAAGGCTTCTGGAGGCACCTTCAGCACCAATTCTATCAACTGGGTGCGACAGGCC
 TGGACAAGGGCTTGAGTGGATGGGAGGGATCATCCCTGTCTTGATGCATCAAATTACGCA
 25 CAGAAGTTCCAGGGCAGAGTCACGATTACCGCGGACGAGTCCACGAGCACAGCCTACATGG
 AGCTGAGCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTTCCCTCAAATTA
 TGATAGTAGTGGTTATTACTTATGATGCTTTGATATCTGGGGCCGAGGCACCCTGGTC
 ACCGTCTCCTCA

30 FAT 37 Heavy Chain Amino Acid sequence SEQ ID NO. 100

Q	V	Q	L	E	Q	S	G	A	E	V	K	K	P	G	S	S	V	K	V	S	
C	K	A	S	G	G	T	F	S	T	N	S	I	N	W	V	R	Q	A	P	G	
Q	G	L	E	W	M	G	G	I	I	P	V	F	D	A	S	N	Y	A	Q	K	
35	F	Q	G	R	V	T	I	T	A	D	E	S	T	S	T	A	Y	M	E	L	S

30

S	L	R	S	E	D	T	A	V	Y	Y	C	S	S	<u>N</u>	<u>Y</u>	<u>Y</u>	<u>Y</u>	<u>D</u>	<u>S</u>	<u>S</u>
G	Y	Y	L	Y	D	A	F	D	I	W	G	R	G	T	L	V	T	V	S	S

FAT 37 Light Chain DNA Sequence SEQ ID NO. 101

5 GATGTTGTGATGACTCAGTCTCCATCTTCCGTGTGCAGCCCCAGGACAGAAAGGTACCCA
 TTTCCCTGCTCTGGAAGCACCTCCAACATTGGGAATAATTATGTCTCCTGGTACCAACAGCA
 CCCAGGCAAAGCCCCAAACTCATGATTTATGATGTCAGTAAGCGGCCCTCAGGGGTCCCT
 GACCGATTCTCTGGCTCCAAGTCTGGCAACTCAGCCTCCCTGGACATCAGTGGCTCCAGT
 10 10 CTGAGGATGAGGCTGATTATTACTGTGCAGCATGGGATGACAGCCTGAGTGAATTCTCTT
 CGGAACCTGGGACCAAGCTGACCGTCCTAGGT

FAT 37 Light Chain Amino Acid Sequence SEQ ID NO. 102

15	D	V	V	M	T	Q	S	P	S	S	V	S	A	A	P	G	Q	K	V	T	I
	S	C	S	G	S	T	S	N	I	G	N	N	Y	V	S	W	Y	Q	Q	H	P
	G	K	A	P	K	L	M	I	Y	D	V	S	K	R	P	S	G	V	P	D	R
	F	S	G	S	K	S	G	N	S	A	S	L	D	I	S	G	L	Q	S	E	D
	E	A	D	Y	Y	C	A	A	W	D	D	S	L	S	E	F	L	F	G	T	G
20	T	K	L	T	V	L															

FAT 38 Heavy Chain DNA Sequence SEQ ID NO. 103

25 GAGGTGCAGCTGGTGGAGACCGGGCTGAGGTGAAGAAGCCTGGTCCTCGGTGAAGGTCT
 CCTGCAAGGCTTCTGGATACACCTTCACCAGTTATGATTTCAACTGGGTGCGACAGGCCAC
 TGGACAAGGGCTTGAGTGGATGGATGAACCTAACAGTGGTACACAGGCTACGCA
 CAGAAGTTCCAGGGCAGAGTCACCATGACCGAGGACACATCTACAGACACAGCCTACATGG
 AGCTGAGGAGCCTGAGACCTGACGACTCGGCCGTATTACTGTGCAGGTGAGGCCGATTG
 TAGTGGTACCTGCTATTCTCTTAACACTGGGGAAAGGGACCACGGTACCGTCTCC
 30 TCA

FAT 38 Heavy Chain Amino Acid sequence SEQ ID NO. 104

35	E	V	Q	L	V	E	T	G	A	E	V	K	K	P	G	S	S	V	K	V	S
	C	K	A	S	G	Y	T	F	T	S	Y	D	F	N	W	V	R	Q	A	T	G

31

Q	G	L	E	W	M	G	W	M	N	P	N	S	G	D	T	G	Y	A	Q	K
F	Q	G	R	V	T	M	T	E	D	T	S	T	D	T	A	Y	M	E	L	R
S	L	R	P	D	D	S	A	V	Y	Y	C	A	V	<u>W</u>	P	D	C	S	G	T
<u>S</u>	C	<u>Y</u>	S	P	N	<u>Y</u>	W	G	K	G	T	T	V	T	V	S	S			

5

FAT 38 Light Chain DNA and Amino Acid sequences

Identical to FAT 31 (SEQ ID NO.'s 87 and 88)

10 FAT 39 Heavy Chain DNA Sequence SEQ ID NO. 105

GAGGTGCAGCTGGTGGAGTCTGGGGCTGAGGTGAAGAAGCCTGGTCCTCGGTGAAGGTCT
 CCTGCAAGGCTTCTGGAGGCACCTCGGCAACTATGGTATCGACTGGGTGCGACTGGCCCC
 TGGACAAAGGACTTGAGTGGATGGGAGGGATCATCCCTCTTTCTGACAACAAATTACGCA
 15 CAGAAGTTCCAGGGCAGAGTCACGATTACCGCGGACGAATCCACGAGCACGGCTTACATGG
 AGATGAGCAGTCTGAGATCTGACGACACGGCCGTGTATTATTGTGCGAGATATGATGCTCG
 TGGTTATTATTATTGGACTTCTGGGGCAAGGGCACCCCTGGTCACCGTCTCGAGT

20 FAT 39 Heavy Chain Amino Acid sequence SEQ ID NO. 106

E	V	Q	L	V	E	S	G	A	E	V	K	K	P	G	S	S	V	K	V	S	
C	K	A	S	G	G	T	F	G	N	Y	G	I	D	W	V	R	L	A	P	G	
Q	G	L	E	W	M	G	G	I	I	P	L	F	R	T	T	N	Y	A	Q	K	
F	Q	G	R	V	T	I	T	A	D	E	S	T	S	T	A	Y	M	E	M	S	
25	S	L	R	S	D	D	T	A	V	Y	Y	C	A	R	<u>Y</u>	D	A	R	G	Y	Y
	<u>Y</u>	L	D	F	W	G	K	G	T	L	V	T	V	S	S						

30 FAT 39 Light Chain DNA and Amino Acid sequences

Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

FAT 40 Heavy Chain DNA Sequence SEQ ID NO. 107

35

CAGGTGCAGCTGCAGGAGTCGGGTCCAAGACTGGTGAAGCCTCGGGGACCTGTCCCTCA
 CATGCGCTGTCTCTGGTGCCTCCATCTATAGCACTAATTCTACAGTTGGTCCGCCAGCC
 CCCAGGGAAGGGCCTGGAGTGGATTGGAGAAATCTCTCTAGTGGGGCATCAACTACAAAC
 CCGTCCCTCAGCAGTCGAGTCACCATATCAATGGACAAGTCCAAGAACAGATCTCCCTGC
 5 AGATGACCTCTGTGACCGCCGCGACACGGCCATGTATTACTGTGCGAGGGGTACAAC
 GCACTACGATGATGCTTGATATCTGGGCCAGGGACAATGGTCACCGTCTCGAGT

FAT 40 Heavy Chain Amino Acid sequence SEQ ID NO. 108

10	Q	V	Q	L	Q	E	S	G	P	R	L	V	K	P	S	G	T	L	S	L	T
	C	A	V	S	G	A	S	I	Y	S	T	N	F	Y	S	W	V	R	Q	P	P
	G	K	G	L	E	W	I	G	E	I	S	L	S	G	G	I	N	Y	N	P	S
	L	S	S	R	V	T	I	S	M	D	K	S	K	N	Q	I	S	L	Q	M	T
	S	V	T	A	A	D	T	A	M	Y	Y	C	A	R	<u>G</u>	Y	N	W	H	Y	D
15	<u>D</u>	A	F	<u>D</u>	<u>I</u>	W	G	Q	G	T	M	V	T	V	S	S					

FAT 40 Light Chain DNA and Amino Acid sequences

Identical to FAT 11 (SEQ ID NO.'s 35 and 36)

20

FAT 41 Heavy Chain DNA Sequence SEQ ID NO. 109

CAGGTGCAGCTGGTGCAGTCTGGGCTGAGGTGAAGAAGCCTGGTCCTCGGTGAAGGTCT
 CCTGCAAGGCTTCTGGAGGCACCTCAGCAGCTATGCTATCAGCTGGTGCACAGGCC
 TGGACAAGGGCTTGAGTGGATGGGAGGGATCATCCCTATCTTGGTACAGCAAAC TACGCA
 CAGAAGTTCCAGGGCAGAGTCACGATTACCGCGACGAATCCACGAGCACAGCCTACATGG
 AGCTGAGCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAGAGGGCTAGCCT
 30 CAACCTATGGCCGGACCCGACGTGGCTTTGATATCTGGGCCGAGGCACTCTGGTCACC
 GTCTCGAGT

FAT 41 Heavy Chain Amino Acid sequence SEQ ID NO. 110

33

Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	S	S	V	K	V	S	
C	K	A	S	G	G	T	F	S	S	Y	A	I	S	W	V	R	Q	A	P	G	
Q	G	L	E	W	M	G	G	I	I	P	I	F	G	T	A	N	Y	A	Q	K	
F	Q	G	R	V	T	I	T	A	D	E	S	T	S	T	A	Y	M	E	L	S	
5	S	L	R	S	E	D	T	A	V	Y	Y	C	A	R	<u>E</u>	<u>A</u>	<u>S</u>	<u>L</u>	<u>N</u>	<u>L</u>	<u>W</u>
	P	D	P	T	W	A	F	D	<u>I</u>	W	G	R	G	T	L	V	T	V	S	S	

FAT 41 Light Chain DNA and Amino Acid sequences

10 Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

FAT 42 Heavy Chain DNA Sequence SEQ ID NO. 111

CAGGTGCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAGCCTGGTCCTCGGTGAAGGTCT
 15 TCTGCAAGGCTTCTGGAGGCACCTTCAGCAGCTATGCTATCAGCTGGGTGCGACAGGCC
 TGGACAAGGGCTTGAGTGGATGGGAGGGATCATCCCTATCTTGGTACAGCAAAC TACGCA
 CAGAAGTTCCAGGGCAGAGTCACGATTACCGCGGACGAATCCACGAGCACAGCCTACATGG
 AGCTGAGCAGCCTGAGATCTGACGACACGCCGTGTATTACTGTGCGAGAGGTAGAGCAGC
 AGCTGACAAA ACTGACTACTGGGCCAAGGCACCCCTGGTCACCGTCTCCTCA

20

FAT 42 Heavy Chain Amino Acid sequence SEQ ID NO. 112

Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	S	S	V	K	V	F	
C	K	A	S	G	G	T	F	S	S	Y	A	I	S	W	V	R	Q	A	P	G	
25	Q	G	L	E	W	M	G	G	I	I	P	I	F	G	T	A	N	Y	A	Q	K
F	Q	G	R	V	T	I	T	A	D	E	S	T	S	T	A	Y	M	E	L	S	
S	L	R	S	D	D	T	A	V	Y	Y	C	A	R	<u>G</u>	<u>R</u>	<u>A</u>	<u>A</u>	<u>A</u>	<u>D</u>	<u>K</u>	
	<u>T</u>	<u>D</u>	<u>Y</u>	W	G	Q	G	T	L	V	T	V	S	S							

30 FAT 42 Light Chain DNA and Amino Acid sequences

Identical to FAT 31 (SEQ ID NO.'s 87 and 88)

FAT 44 Heavy Chain DNA Sequence SEQ ID NO. 113

35

GAGGTCCAGCTGGTGCAGTCTGGGCTGAGGTGAAGAAGCCTGGTCCTCGGTGAAGGTCT
 CCTGCAAGGCTTCTGGAGGCACCTTCAGCAGCTATGCTATCAGCTGGGTGCGACAGGCC
 TGGACAAGGGCTTGAGTGGATGGGAGGGATCATCCCTATCTTGGTACAGCAAAC TACGCA
 CAAGAGCTTCAACAGGGAGAGTCACGATTACCGCGAACGAATCCACGAGCACAGCCTACA
 5 TGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCCGCGTATTACTGTGCGAGAAAGGGCT
 AGACCGAACCTACTACATGGACGTCTGGGGCAGGTCGAGTCCTGGGCAGGGGACCA C
 GTCACCGTCTCTTCA

10 FAT 44 Heavy Chain Amino Acid sequence SEQ ID NO. 114

E	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	S	S	V	K	V	S	
C	K	A	S	G	G	T	F	S	S	Y	A	I	I	S	W	V	R	Q	A	P	G
Q	G	L	E	W	M	G	G	I	I	P	I	F	G	T	A	N	Y	A	Q	E	
15	L	Q	Q	G	R	V	T	I	T	A	D	E	S	T	S	T	A	Y	M	E	L
S	S	L	R	S	E	D	T	A	A	Y	Y	C	A	R	<u>K</u>	G	L	D	R	T	
<u>Y</u>	<u>Y</u>	<u>M</u>	<u>D</u>	<u>V</u>	<u>W</u>	<u>G</u>	<u>Q</u>	<u>V</u>	<u>E</u>	<u>S</u>	<u>W</u>	<u>G</u>	<u>R</u>	<u>G</u>	<u>T</u>	<u>T</u>	<u>V</u>	<u>T</u>	<u>V</u>	<u>S</u>	

20 FAT 44 Light Chain DNA Sequence SEQ ID NO. 115

CAGTCTGTGTTGACGCAGCCGCCCTCAGTGTCTGCGGCCAGGACAGAAGGTACCCATT
 CCTGCTCTGGAAGCACCTCCAACATTGGAAATAATTATGTCCTGGTACCAACAGCACCC
 AGGCAAAGCCCCGAACTCATGATTATGATGTCAGTAAGCGGCCCTCAGGGTCCCTGAC
 25 CGATTCTCTGGCTCCAAGTCTGGCAACTCAGCCTCCCTGGACATCAGTGGCTCCAGTCTG
 AGGATGAGGCTGATTATTACTGTGCAGCATGGATGACAGCCTGAGTGAATTCTCTTCGG
 AACTGGGACCAAGCTGACCGTCCTA

FAT 44 Light Chain Amino Acid Sequence SEQ ID NO. 116

Q	S	V	L	T	Q	P	P	S	V	S	A	A	P	G	Q	K	V	T	I	S
C	S	G	S	T	S	N	I	G	N	N	Y	V	S	W	Y	Q	Q	H	P	G
K	A	P	E	L	M	I	Y	D	V	S	K	R	P	S	G	V	P	D	R	F
S	G	S	K	S	G	N	S	A	S	L	D	I	S	G	L	Q	S	E	D	E

35

A	D	Y	Y	C	A	A	W	D	D	S	L	S	E	F	L	F	G	T	G	T
K	L	T	V	L																

FAT 45 Heavy Chain DNA sequence SEQ ID NO. 117

5

CAGGTCAACTTAAGGGAGTCTGGGGGAGGCTTGGTACAGCCAGGAGGGTCCCTGAGACTCT
 CCTGCGTAGCCTCTGGATTCACCTTGAGTAATTGACCTGAATTGGTCCGCCAGGCTCC
 AGGGAAGGGGCTGGAGTGGCTTCATACATCAGTAGCAGTGGTCCACAATATCCTACGCA
 GACTCTGTGAGGGGCCGATTCACCATCTCCAGAGACCACGTCAAGAACTCACTATCTCTGC
 10 AAATGAAGAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAAAGGGGGAGCAG
 CCCCGCGGGAGTCGCAGACTACTGGGCCAAGGCACCCCTGGTCACCGTCTCGAGT

FAT 45 Heavy Chain Amino Acid sequence SEQ ID NO. 118

15	Q	V	N	L	R	E	S	G	G	G	L	V	Q	P	G	G	S	L	R	L	S	
	C	V	A	S	G	F	T	L	S	N	F	D	L	N	W	V	R	Q	A	P	G	
	K	G	L	E	W	L	S	Y	I	S	S	S	G	S	T	I	S	Y	A	D	S	
	V	R	G	R	F	T	I	S	R	D	H	V	K	N	S	L	S	L	Q	M	K	
	S	L	R	A	E	D	T	A	V	Y	Y	C	A	K	<u>G</u>	<u>G</u>	<u>S</u>	<u>S</u>	<u>P</u>	<u>A</u>	<u>G</u>	
20	<u>V</u>	<u>A</u>	<u>D</u>	<u>Y</u>	<u>W</u>	<u>G</u>	<u>Q</u>	<u>G</u>	<u>T</u>	<u>L</u>	<u>V</u>	<u>T</u>	<u>V</u>	<u>S</u>	<u>S</u>							

FAT 45 Light Chain DNA and Amino Acid sequences

Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

25

FAT 46 Heavy Chain DNA sequence SEQ ID NO. 119

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGTGTGGTACGGCCTGGGGGTCCCTGAGACTCT
 CCTGTGCAGCCTCTGGATTACACCTTGATGATTATGGCATGAGCTGGTCCGCCAAGCTCC
 30 AGGGAAGGGCTGGAGTGGTCTCTGGTATTAATTGGAATGGTGGTAGCACAGGTTATGCA
 GACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCCCTGTATGTGC
 AAATGAACAGTCTGAGAGCCGAGGACACGGCCTTGTATCACTGTGCGAGCTCTATGATCGA
 AGGTGCTTTGATATCTGGGCCAAGGGACAATGGTCACCGTCTCGAGT

35 FAT 46 Heavy Chain Amino Acid sequence SEQ ID NO. 120

36

E	V	Q	L	V	E	S	G	G	G	V	V	R	P	G	G	S	L	R	L	S	
C	A	A	S	G	F	T	F	D	D	Y	G	M	S	W	V	R	Q	A	P	G	
K	G	L	E	W	V	S	G	I	N	W	N	G	G	S	T	G	Y	A	D	S	
V	K	G	R	F	T	I	S	R	D	N	A	K	N	S	L	Y	V	Q	M	N	
5	S	L	R	A	E	D	T	A	L	Y	H	C	A	S	<u>S</u>	<u>M</u>	<u>I</u>	<u>E</u>	<u>G</u>	<u>A</u>	<u>F</u>
	<u>D</u>	<u>I</u>	<u>W</u>	<u>G</u>	<u>Q</u>	<u>G</u>	<u>T</u>	<u>M</u>	<u>V</u>	<u>T</u>	<u>V</u>	<u>S</u>	<u>S</u>								

FAT 46 Light Chain DNA and Amino Acid sequences

10 Identical to FAT 44 (SEQ ID NO.'s 115 and 116)

FAT 48 Heavy Chain DNA Sequence SEQ ID NO. 121

GAGGTGCAGCTGGTGCAGTCTGGGGGAGGCGTGGTCCAGCCTGGAGGTTCCCGGAAACTCT
15 CCTGTGCAGCCTCTGGATTCACCTTAGCAGCTATGCCATGAGCTGGTCCGCCAGGCTCC
AGGGAAGGGGCAGGAGTGGGTCTCAGCTATTAGTGGTAGTGGTGGTAGCGCATACTACGCA
GACTCCGTGAAGGGCCGGTTACCATTCCAGAGACAATTCCAAGAACACGCTGTATCTGC
AAATGAACAGCCTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAGCCTATAGCAG
TGAAGACTACTGGGGCCAAGGAACCCTGGTCACCGTCTCCTCA

20

FAT 48 Heavy Chain Amino Acid sequence SEQ ID NO. 122

E	V	Q	L	V	Q	S	G	G	G	V	V	Q	P	G	G	S	R	K	L	S	
C	A	A	S	G	F	T	F	S	S	Y	A	M	S	W	V	R	Q	A	P	G	
K	G	Q	E	W	V	S	A	I	S	G	S	G	G	S	A	Y	Y	A	D	S	
V	K	G	R	F	T	I	S	R	D	N	S	K	N	T	L	Y	L	Q	M	N	
30	S	L	R	A	E	D	T	A	V	Y	Y	C	A	K	<u>A</u>	<u>Y</u>	<u>S</u>	<u>S</u>	<u>E</u>	<u>D</u>	<u>Y</u>
	W	G	Q	G	T	L	V	T	V	S	S										

FAT 48 Light Chain DNA and Amino Acid sequences

35

Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

FAT 49 Heavy Chain DNA Sequence SEQ ID NO. 123

5 CAGGTCACCTTGAAGGAGTCTGGGGAGGCTTGTCCAGCCTGGGGTCCCTGAGACTCT
 CCTGTGCAGCTTCTGGATTACCTTACTAGCAATTGGATGAGCTGGTCCGCCAGGCTCC
 AGGGAAGGGGCTGGAGTGGGTTCAACTATCAGTGATAGTGGTGGTCTCACACATTCCGCA
 GACTCCCTGAAGGGCCGGCCACCGTCCCCAGAGACAATTCCGAGAACACGATGTATCTGG
 AACTGCGCAGGCTGAGAGCCGACGACTCGCCAATTATTACTGTGCTAGAGGTCTTACCGT
 10 TTTTGGCGTAGTCAATGCTCTTGATGTCTGGGCAAGGAAACCTGGTCACCGTCTCCTCA

FAT 49 Heavy Chain Amino Acid sequence SEQ ID NO. 124

Q	V	T	L	K	E	S	G	G	G	L	F	Q	P	G	G	S	L	R	L	S	
15	C	A	A	S	G	F	T	F	S	S	N	W	M	S	W	V	R	Q	A	P	G
	K	G	L	E	W	V	S	T	I	S	D	S	G	G	L	T	H	S	A	D	S
	L	K	G	R	A	T	V	P	R	D	N	S	E	N	T	M	Y	L	E	L	R
	G	L	R	A	D	D	S	A	N	Y	Y	C	A	R	<u>G</u>	<u>L</u>	<u>T</u>	<u>V</u>	<u>F</u>	<u>G</u>	<u>V</u>
20	V	N	A	L	D	V	W	G	K	G	T	L	V	T	V	S	S				

FAT 49 Light Chain DNA and Amino Acid sequences

Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

25 FAT 50 Heavy Chain DNA Sequence SEQ ID NO. 125

CAGGTGCAGCTGCAGCAGTCGGACCTGGCCTGGTGGGCCCTCACAGAGCCTGTCCGTCA
 CATGCACCGTCTCAGGGTTCTCATTAACCGGCTATGGTGTAAACTGGGTTGCCAGCCTCC
 AGGAAAGGGTCTGGAGTGGCTGGGAATGATTGGGGTGTGGAAACACAGACTATAATTCA
 30 GCTCTCAAATCCAGACCGAGCATCAGCAAGGACAACCTCAAGAGCCAAGTTTCTTAAAAA
 TGAACAGTCTGCACACTGATGACACAGCCAGGTACTACTGTGCCAGAGAGAGATTATAG
 GCTTGACTACTGGGGCCGAGGGACAATGGTCACGTCT

FAT 50 Heavy Chain Amino Acid sequence SEQ ID NO. 126

Q	V	Q	L	Q	Q	S	G	P	G	L	V	A	P	S	Q	S	L	S	V	T	
C	T	V	S	G	F	S	L	T	G	Y	G	V	N	W	V	R	Q	P	P	G	
K	G	L	E	W	L	G	M	I	W	G	D	G	N	T	D	Y	N	S	A	L	
K	S	R	P	S	I	S	K	D	N	S	K	S	Q	V	F	L	K	M	N	S	
5	L	H	T	D	D	T	A	R	Y	Y	C	A	R	<u>E</u>	R	D	Y	R	L	D	Y
	W	G	R	G	T	M	V	T	S												

10 FAT 50 Light Chain DNA and Amino Acid sequences

Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

15 FAT 52 Heavy Chain DNA Sequence SEQ ID NO. 127

CAGGTACAGCTGCAGCAGTCAGGAAC	TGAGGTGAAGAGAC	CTGGGGCCTCAGTGAAGGTCT
CCTGCAAGACTTCTGGCTACAC	CTTCCCAGTTATGGTATCAG	CTGGGTGCGACAGGCC
TGGACAAGGGCTTGAGTGGATGG	ATCAACTGTTACAATGGTAA	TACAAACTATGCA
CAGAGCTTCCAGGACAGAGTCACC	ATGACCGCAGACACATCCAC	CGACTACAGCCTACATGG
20 AGGTGAGGAAGCTGAAGTCTGAC	GACACGGCCGTGTATTCTGT	CGAGGTCGCTCGTCCC
AACCAACTGTGACA	ACACTGGGCCGAAGCACCCTGG	TACCGTCTCCTCA

25 FAT 52 Heavy Chain Amino Acid sequence SEQ ID NO. 128

Q	V	Q	L	Q	Q	S	G	T	E	V	K	R	P	G	A	S	V	K	V	S
C	K	T	S	G	Y	T	F	P	S	Y	G	I	S	W	V	R	Q	A	P	G
Q	G	L	E	W	M	G	W	I	N	C	Y	N	G	N	T	N	Y	A	Q	S
F	Q	D	R	V	T	M	T	A	D	T	S	T	T	T	A	Y	M	E	V	R
K	L	K	S	D	D	T	A	V	Y	F	C	A	R	<u>S</u>	L	V	P	T	N	C
30 D	N	W	G	R	S	T	L	V	T	V	S	S								

35 FAT 52 Light Chain DNA and Amino Acid sequences

Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

FAT 53 Heavy Chain DNA Sequence SEQ ID NO. 129

5 CAGGTGCAGCTGTTGCAGTCTGGAGCAGAGGTGAAAAAGCCGGGGACTCTCTGAAGATCT
 CCTGTAAGGCTTCTGGATACAACCTTCCAACTCTTGGATCGGCTGGGTGCGCCAGATGCC
 CGGGAAGGGCCTGGAGTACATGGGGCTCATCTATCCTGGTACTCTGACACCAAATACAGC
 CCGTCCTCCAAGGCCAGGACACCATGTCAGTCAGAAGTCCGTCAGCACTGCCTACTTGC
 AATGGAGCAGTCTGAGGCCCTCGGACAGCGCCGTGTATTTGTGCGAGACATGACGTGGG
 ATATTGCAGTAGTTCCAAC TGCGCAAGGAGGCCTGAATAACTCCAGCATTGGGCCGAGGA
 10 ACCCTGGTCACCGTCTCCTCA

FAT 53 Heavy Chain Amino Acid sequence SEQ ID NO. 130

Q	V	Q	L	L	Q	S	G	A	E	V	K	K	P	G	D	S	L	K	I	S	
15	C	K	A	S	G	Y	N	F	P	N	S	W	I	G	W	V	R	Q	M	P	G
	K	G	L	E	Y	M	G	L	I	Y	P	G	D	S	D	T	K	Y	S	P	S
	F	Q	G	Q	D	T	M	S	V	D	K	S	V	S	T	A	Y	L	Q	W	S
	S	L	R	P	S	D	S	A	V	Y	F	C	A	R	<u>H</u>	<u>D</u>	<u>V</u>	<u>G</u>	<u>Y</u>	<u>C</u>	<u>S</u>
	S	S	N	C	A	R	R	P	E	Y	F	Q	H	W	G	R	G	T	L	V	T
20	V	S	S																		

FAT 53 Light Chain DNA and Amino Acid sequences

Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

25

FAT 54 Heavy Chain DNA Sequence SEQ ID NO. 131

30 CAGATGCAGCTGGTGCAGTTGGGGCTGAGGTGAAGAAGCCTGGTCCTCGGTGAAGGTCT
 CCTGCAAGGCTTCTGGAGGCACCTCAGCAGTTATGCTATCAGCTGGGTGCGACAGGCC
 TGGACAAGGGCTTGAGTGGATGGGAGGGTCATCCCTATCTTGATACAGCAAAC TACGCA
 CAGAACGTTCCAGGGCAGAGTCACGATTACCGCGGACGAATCCACGAGCACAGCCTACATGG
 AGCTGAGCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAGATGCCTCCAT
 ACCCGATGATA CATGGACTACTGGGGCAGAGGGACAATGGTCACGGTCTCGAGT

35 FAT 54 Heavy Chain Amino Acid sequence SEQ ID NO. 132

40

Q	M	Q	L	V	Q	F	G	A	E	V	K	K	P	G	S	S	V	K	V	S	
C	K	A	S	G	G	T	F	S	S	Y	A	I	S	W	V	R	Q	A	P	G	
Q	G	L	E	W	M	G	G	F	I	P	I	F	D	T	A	N	Y	A	Q	K	
F	Q	G	R	V	T	I	T	A	D	E	S	T	S	T	A	Y	M	E	L	S	
5	S	L	R	S	E	D	T	A	V	Y	Y	C	A	R	<u>D</u>	A	S	I	P	D	D
	<u>T</u>	<u>W</u>	<u>D</u>	<u>Y</u>	W	G	R	G	T	M	V	T	V	S	S						

FAT 54 Light Chain DNA and Amino Acid sequences

10 Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

FAT 55 Heavy Chain DNA Sequence SEQ ID NO. 133

CAGGTGCAGCTGCAGGAGTCCGGCCCAGGAATGGGTGGAGCCCTTCGGAGACCCTGTCCC
 15 TCACCTGCTCTGTCCTGGTGACTCCATCTCCAGTGGTGGTTACTCCTGGAGCTGGATCCG
 GCAGCCATCAGGGAAGGGACTGGAGTGGGTCTTCCATTAGTAGCAATAATCGGTTCTA
 TACTACGCAGACTCAGTGCAGGGCCGATTCAACCATCTCCAGAGACAACCCCAAAACTCAC
 TGTCTCTGCAAATGAGCAGTCTGAGAGCCGAGGACACGGCTGTCTACTACTGTGCGAGAGG
 TCAGCGCCTGTACATTGACTCCTGGGCCGAGGCACCCCTGGTCACGGTCTCCTCA

20

FAT 55 Heavy Chain Amino Acid sequence SEQ ID NO. 134

25 Q V Q L Q E S G P G M G G A L S E T L S L
 T C S V S G D S I S S G G Y S W S W I R Q
 P S G K G L E W V S S I S S N N R F I Y Y
 A D S V Q G R F T I S R D N P K N S L S L
 Q M S S L R A E D T A V Y Y C A R G Q R L
 30 Y I D S W G R G T L V T V S S

FAT 55 Light Chain DNA and Amino Acid sequences

Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

35

FAT 56 Heavy Chain DNA Sequence SEQ ID NO. 135

CAGGTACAGCTGCAGCAGTCAGGTCCAGGACTGGTGAAGCCTTGCAGACCCCTCACTCA
 CCTGTGCCATTCCGGGGACAGTGTGCTAGTAACAGTGCTGCTGGAACTGGATCAGGCA
 5 GTCCCCCTCGAGAGGCCTTGAGTACCTGGGAAGGACATACTACAGGTCCAGGTGGTACACT
 GAATATGCAGTGCCTGTGAAAAGTCGCATAACCATAACCCGACACATCCAGGAACCAGT
 ACTCCCTGCAGCTGAATTCTGTGACTCCGAGGACACGGCCGTGTATTACTGTGCAAGAGA
 CGGTTCGCTGGGCTTGATGCTTTGATATCTGGGCCAAGGAACCCTGGTCACCGTCT

10 FAT 56 Heavy Chain Amino Acid sequence SEQ ID NO. 136

Q	V	Q	L	Q	Q	S	G	P	G	L	V	K	P	L	Q	T	P	S	L	T	
C	A	I	S	G	D	S	V	A	S	N	S	A	A	W	N	W	I	R	Q	S	
P	S	R	G	L	E	Y	L	G	R	T	Y	Y	R	S	R	W	Y	T	E	Y	
15	A	V	P	V	K	S	R	I	T	I	N	P	D	T	S	R	N	Q	Y	S	L
Q	L	N	S	V	T	P	E	D	T	A	V	Y	Y	C	A	R	<u>D</u>	<u>G</u>	<u>S</u>	<u>L</u>	
	G	L	D	A	L	D	<u>I</u>	W	G	Q	G	T	L	V	T	V					

FAT 56 Light Chain DNA and Amino Acid sequences

20 Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

FAT 57 Heavy Chain DNA sequence SEQ ID NO. 137

25 CAAGTCACCTGAAGGAGTCTGGGGCTGAGGTGAAGAAGTCTGGGTCTCGGTGAAGGTCT
 CCTGCAAGGCTTCTGGAGACAGCTCAATAGCCACGCTATCAACTGGGTGCGACAGGGCCC
 TGGACAAGGGCTTGAGTGGATGGGAGGGATCATCCCTTGTGTTACTGCAAAGTACGCA
 CAGCAGTTCCAGGGCAGAGTCACAATTACCGCGGACGAATCCACGAACCCAGCCTACATGG
 AGCTGAGCAGCCTGAGATCTGAGGACACGGCCGTGTTACTGTGCGAGAGGAAAGTACGC
 30 TGGTAATTCCGGTCGGCACGGTATGGACGTCTGGGCCAGGGACAATGGTCACGGTCTCG
 AGT

FAT 57 Heavy Chain Amino Acid sequence SEQ ID NO. 138

42

Q	V	T	L	K	E	S	G	A	E	V	K	K	S	G	S	S	V	K	V	S	
C	K	A	S	G	D	S	F	N	S	H	A	I	N	W	V	R	Q	G	P	G	
Q	G	L	E	W	M	G	G	I	I	P	L	F	G	T	A	K	Y	A	Q	Q	
F	Q	G	R	V	T	I	T	A	D	E	S	T	N	P	A	Y	M	E	L	S	
5	S	L	R	S	E	D	T	A	V	F	Y	C	A	R	<u>G</u>	<u>K</u>	<u>Y</u>	<u>A</u>	<u>G</u>	<u>N</u>	<u>S</u>
	<u>G</u>	<u>R</u>	<u>H</u>	<u>G</u>	<u>M</u>	<u>D</u>	<u>V</u>	<u>W</u>	<u>G</u>	<u>Q</u>	<u>G</u>	<u>T</u>	<u>M</u>	<u>V</u>	<u>T</u>	<u>V</u>	<u>S</u>	<u>S</u>			

10 FAT 57 Light Chain DNA and Amino Acid sequences

Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

FAT 58 Heavy Chain DNA Sequence SEQ ID NO. 139

15 GAGGTGCAGCTGGTGCCTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCT
 CCTGTGCAGCCTCTGGATTCACCTTCAGTGACTACTACATGAGCTGGATCCGCCAGGCTCC
 AGGGAAGGGGCTGGAGTGGGTTTCATACATTAGTAGTAGTAGTTACACAAACTACGCA
 GACTCTGTGAAGGGCCGATTACCACATCTCCAGAGACAACGCCAAGAACTCACTGTATCTGC
 20 AAATGAACAGCCTGAGAGCCGAGGACACGCCGTGTATTACTGTGCGAGAGATCGTATAG
 TAGTGGTTATCACATCTGGGCCAGGGACAATGGTCACGGTCTCTCA

FAT 58 Heavy Chain Amino Acid sequence SEQ ID NO. 140

25 E V Q L V R S G G G L V K P G G S L R L S
 C A A S G F T F S D Y Y M S W I R Q A P G
 K G L E W V S Y I S S S S Y T N Y A D S
 V K G R F T I S R D N A K N S L Y L Q M N
 30 S L R A E D T A V Y Y C A R D R D S S G Y
 H I W G Q G T M V T V S S

FAT 58 Light Chain DNA and Amino Acid sequences

Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

FAT 59 Heavy Chain DNA Sequence SEQ ID NO. 141

5 CAGGTCACCTTGAAGGAGTCTGGGGAGAATTGGTCCAGCCTGGGGGTCCCCGAGACTCT
 CCTGTTCAGCCTCTGGATTCACCTTCAGTAGTCTTGCTATGCACTGGGTCCGCCAGGCTCC
 AGGGAGGGGACTGGAATATGTTCCATTAGTAATGGTGATGGGACTAGCACAACCTACGCA
 GACTCCGTGAAGGGCAGATTCAACCACATCCAGAGACAATTCCAAGAACACGATGTATCTC
 AAATGAACAGTCTGAGACCTGAGGACACGGCTGTGTATTACTGTGTGAGAGATGTTACGG
 10 CATGGACGTCTGGGCAGAGGCACCCCTGGTCACCGTCTCCTCA

FAT 59 Heavy Chain Amino Acid sequence SEQ ID NO. 142

Q	V	T	L	K	E	S	G	G	E	L	V	Q	P	G	G	S	P	R	L	S	
15	C	S	A	S	G	F	T	F	S	S	L	A	M	H	W	V	R	Q	A	P	G
	R	G	L	E	Y	V	S	I	S	N	G	D	G	T	S	T	T	Y	A	D	S
	V	K	G	R	F	T	T	S	R	D	N	S	K	N	T	M	Y	L	Q	M	N
	S	L	R	P	E	D	T	A	V	Y	Y	C	V	R	D	V	Y	G	M	D	V
20	W	G	R	G	T	L	V	T	V	S	S										

FAT 59 Light Chain DNA and Amino Acid sequences

Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

FAT 60 Heavy Chain DNA sequence SEQ ID NO. 143

CAGGTCACCTTGAAGGAGTCTGGGGCTGAGGTGGAGAAACCTGGGCCTCAGTGAAGGTTT
 CCTGCAAGGCCTCTGGATACAGTTCACTAACTATGCTATTCAATTGGGTGCCAGGCC
 CGGACAAAGGCTTGAGTGGATGGATCAACGCTGGCAATGGTACACAACATATTCA
 30 CAGAGGTTCCAGGGCAGAGTCAACATGACCAAGGACACATCTACAGAGACAGCCTACATGG
 AGCTGCGCAGCCTGAGACCTGAGGACACGGCCGTGTATTATTGTACCGAAGGGAGCGGGGA
 TGTGGATACAGATATGATAACCAGTGATGCTGTTGATATCTGGGGCAAGGGAACCCCTGGTC
 ACCGTCTCCTCA

FAT 60 Heavy Chain Amino Acid sequence SEQ ID NO. 144

44

Q	V	T	L	K	E	S	G	A	E	V	E	K	P	G	A	S	V	K	V	S	
C	K	A	S	G	Y	S	F	T	N	Y	A	I	H	W	V	R	Q	A	P	G	
Q	R	L	E	W	M	G	W	I	N	A	G	N	G	D	T	T	Y	S	Q	R	
F	Q	G	R	V	N	M	T	K	D	T	S	T	E	T	A	Y	M	E	L	R	
5	S	L	R	P	E	D	T	A	V	Y	Y	C	T	R	<u>R</u>	S	G	D	V	D	T
	D	M	I	T	S	D	A	V	D	I	W	G	K	G	T	L	V	T	V	S	S

FAT 60 Light Chain DNA and Amino Acid sequences

10 Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

FAT 61 Heavy Chain DNA Sequence SEQ ID NO. 145

GAGGTGCAGCTGGTGGAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCTCGGTGAAGGTCT	
15 CCTGCAAGGCTTTGGAGGCACCTCGGCAGATATGCAATCACCTGGGTGCAGGCAGGCC	
TGGACAAGGGCTTGAGTGGATGGGAGGGATCATCCCTATGTTGGTACAACGAAATCCGCA	
CAGAAGTTCCAGGGCAGAGTCACGATTACCGCGGACGAATCCACGAGCACAGCCTACATGG	
AGTTGAGCAGCTTGAGATCTGAGGACACGGCCGCGTATTACTGTGCGAGAGATTACTATGA	
TAACGGGGCGACTAACTTGATTACTGGGGCAAGAGGGACAATGGTCACCGTCTCTCA	

20

FAT 61 Heavy Chain Amino Acid sequence SEQ ID NO. 146

25 E	V	Q	L	V	E	S	G	A	E	V	K	K	P	G	S	S	V	K	V	S
C	K	A	F	G	G	T	F	G	R	Y	A	I	T	W	V	R	Q	A	P	G
Q	G	L	E	W	M	G	G	I	I	P	M	F	G	T	T	K	S	A	Q	K
F	Q	G	R	V	T	I	T	A	D	E	S	T	S	T	A	Y	M	E	L	S
S	L	R	S	E	D	T	A	A	Y	Y	C	A	R	<u>D</u>	Y	Y	D	N	G	A
30 T	N	F	D	<u>Y</u>	W	G	K	R	T	M	V	T	V	S	S					

FAT 61 Light Chain DNA and Amino Acid sequences

Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

35

FAT 62 Heavy Chain DNA sequence SEQ ID NO. 147

5 CAGGTGCAGCTGCAGCAGTCAGGGGGGGCTTGGTCCAGCCGGGGGTCCTGAGAATCT
 CCTGTGCAGCCTCTGGATTCACCTCAGTACTACATGAGATGGATCCGCCAGGCTCC
 AGGGAAGGGCTGGAGTGGGTTCAAACATTAGTTCTAGTGGTAGTAGCATATACTACGCA
 GACTACATGTTCAGGACTAATTCAACACTTACTGTAGACACATCCTCCAGTACAGCCTACA
 TGCAGCTCAGCAGCCTGACATCTGAGGACTCTGCGGTCTATTATTGTTCAAGAGGGGACGG
 CAGTGATTATTATGCTATGGACTACTGGGCAGAGGAACCCTGGTCACCGTCTCCTCA

10 FAT 62 Heavy Chain Amino Acid sequence SEQ ID NO. 148

Q	V	Q	L	Q	Q	S	G	G	L	V	Q	P	G	G	S	L	R	I	S		
C	A	A	S	G	F	T	S	S	D	Y	Y	M	R	W	I	R	Q	A	P	G	
K	G	L	E	W	V	S	N	I	S	S	S	G	S	S	I	Y	Y	A	D	Y	
15	M	F	R	T	N	S	T	L	T	V	D	T	S	S	S	T	A	Y	M	Q	L
S	S	L	T	S	E	D	S	A	V	Y	Y	C	S	R	<u>G</u>	<u>D</u>	<u>G</u>	<u>S</u>	<u>D</u>	<u>Y</u>	
<u>Y</u>	<u>A</u>	<u>M</u>	<u>D</u>	<u>Y</u>	<u>W</u>	<u>G</u>	<u>R</u>	<u>G</u>	<u>T</u>	<u>L</u>	<u>V</u>	<u>T</u>	<u>V</u>	<u>S</u>	<u>S</u>						

FAT 62 Light Chain DNA and Amino Acid sequences

20

Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

FAT 63 Heavy Chain DNA sequence SEQ ID NO. 149

25 CAGGTACCTTGAAGGAGTTGAGGGAGGCGTGGTCCAGCCTGGAGGTCCCTGAGACTCT
 CCTGTGCAGCCTCTGGATCTAATTCAAGTTAGTTATGGCATGCAGTGGGTCCGCCAGGCTCC
 AGGCAAGGGCTGGAGTGGGTGACAGTTATATCATATGATGGAAGTGATAAAACTATGCA
 GACTCCGTGAAGGCCAATTCATGCCCTCCAGAGACAATTCCAAGAACTCCCTGTATCTGC
 AAATGAACAGCCTGAGAGCCGAGGACACGGCTGTTATTACTGTGCGAGAGATGGACAAC
 30 TAGAACGACGCCACGGACTACATGGACGTCTGGGGAAAGGGACCACGGTACCGTCTCT
 TCT

FAT 63 Heavy Chain Amino Acid sequence SEQ ID NO. 150

46

Q	V	T	L	K	E	F	E	G	G	V	V	Q	P	G	R	S	L	R	L	S	
C	A	A	S	G	S	N	F	S	S	Y	G	M	H	W	V	R	Q	A	P	G	
K	G	L	E	W	V	T	V	I	S	Y	D	G	S	D	K	Y	Y	A	D	S	
V	K	G	Q	F	I	A	S	R	D	N	S	K	N	S	L	Y	L	Q	M	N	
5	S	L	R	A	E	D	T	A	V	Y	Y	C	A	R	<u>D</u>	G	T	T	R	T	T
	<u>A</u>	<u>T</u>	<u>D</u>	<u>Y</u>	<u>M</u>	<u>D</u>	<u>V</u>	<u>W</u>	<u>G</u>	<u>K</u>	<u>G</u>	<u>T</u>	<u>T</u>	<u>V</u>	<u>T</u>	<u>V</u>	<u>S</u>	<u>S</u>			

10 FAT 63 Light Chain DNA and Amino Acid sequences

Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

15 FAT 64 Heavy Chain DNA sequence SEQ ID NO. 151

CAGGAGCAGATGCAGGAGTCGGGGGTGAGGTGAAGAAGCCTGGTCCTCGGTGGGGTGT
 CCTGCAAGGCTTCAGGAGGCACATTTCAGCAGCTATGCTATCAGCTGGATGCGACAGGCC
 TGGACAAGGGCTTGAGTGGATGGATGGATGAACCTAACAGTGGTAACACAGGGCTATGCA
 CAGAAGTTCCAGGGCAGAGTCACCATGACCAGGAACACCTCCATAAGCACAGCCTACATGG
 20 AGCTGAGCAGCCTGAGATCTGAGGACGCGGCCGTCTATTACTATGCGAGACCCGGTGGTT
 GGGAGCAGCTCGTCCTTTGACTATTGGGGCGAGAGACCACGGTCACGGTTCTTCG

25 FAT 64 Heavy Chain Amino Acid sequence SEQ ID NO. 152

Q	E	Q	M	Q	E	S	G	G	E	V	K	K	P	G	S	S	V	G	V	S	
C	K	A	S	G	G	T	F	S	S	Y	A	I	S	W	M	R	Q	A	P	G	
Q	G	L	E	W	M	G	W	M	N	P	N	S	G	N	T	G	Y	A	Q	K	
F	Q	G	R	V	T	M	T	R	N	T	S	I	S	T	A	Y	M	E	L	S	
S	L	R	S	E	D	A	A	V	Y	Y	A	R	<u>P</u>	<u>G</u>	<u>G</u>	<u>L</u>	<u>G</u>	<u>A</u>	<u>A</u>		
30	<u>R</u>	<u>P</u>	<u>F</u>	<u>D</u>	<u>Y</u>	<u>W</u>	<u>G</u>	<u>R</u>	<u>E</u>	<u>T</u>	<u>T</u>	<u>V</u>	<u>T</u>	<u>V</u>	<u>S</u>	<u>S</u>					

35 FAT 64 Light Chain DNA Sequence SEQ ID NO. 153

CAGTCTGTGCTGACTCAGCCTGCCTCCGTCTGGGCCTCCTGGACAGTCAGTCACCAC
 CCTGCAGTGGAACCAACAGCAGTGACATTGGTAGTTAACTATGTCCTGGTACCAACAACA

CCCAGGCGAAGCCCCAAACTCATGATTTATGAGGTCACTAAGCGGCCCTCAGGGGTCCCT
 GATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCGTCTCTGGGCTCCAGG
 CTGAGGATGAGGCTGATTATTACTGCAGCTCATATGCAGGCAGCAACACTGTAATTCGG
 CGGAGGGACCAAGGTCACCGTCCTA

5

FAT 64 Light Chain Amino Acid sequence SEQ ID NO. 154

Q	S	V	L	T	Q	P	A	S	V	S	G	P	P	G	Q	S	V	T	I	S	
C	T	G	T	S	S	D	I	G	S	Y	N	Y	V	S	W	Y	Q	Q	H	P	
10	G	E	A	P	K	L	M	I	Y	E	V	T	K	R	P	S	G	V	P	D	R
	F	S	G	S	K	S	G	N	T	A	S	L	T	V	S	G	L	Q	A	E	D
	E	A	D	Y	Y	C	S	S	Y	A	G	S	N	T	V	I	F	G	G	G	T
	K	V	T	V	L																

15 FAT 65 Heavy Chain DNA Sequence SEQ ID NO. 155

CAGGTGCAGCTGGTGGAGACCGGGGGAGGCTTGGTCAAGCCTGGAGGGCCCTGAGACTTT
 CCTGTGCAGCCTCTGGATTACCTTCAGTGAATCAGTACTACATGAGCTGGATCCGCCAGGCTCC
 AGGGAAGGGGCTGGAGTGGGCTTCATACATTAGTAGTAGTAGTTACACAAACTACGCA
 20 GACTCTGTGAAGGGCCGATTCAACCATTCCAGAGACAACGCCAAGAACTCACTGTATCTGC
 AAATGAACAGCCTGAGAGCCGAGGACACGCCGTGTATTACTGTGCGAGAGACGCGAGGTG
 GTTCGACCCCTGGGCCAGGGCACCTGGTACCGTCTCGAGT

FAT 65 Heavy Chain Amino Acid sequence SEQ ID NO. 156

25	Q	V	Q	L	V	E	T	G	G	G	L	V	K	P	G	G	P	L	R	L	S
	C	A	A	S	G	F	T	F	S	D	Y	Y	M	S	W	I	R	Q	A	P	G
	K	G	L	E	W	A	S	Y	I	S	S	S	S	S	Y	T	N	Y	A	D	S
	V	K	G	R	F	T	I	S	R	D	N	A	K	N	S	L	Y	L	Q	M	N
30	S	L	R	A	E	D	T	A	V	Y	Y	C	A	R	<u>D</u>	<u>A</u>	<u>R</u>	<u>W</u>	<u>F</u>	<u>D</u>	<u>P</u>
	W	G	Q	G	T	L	V	T	V	S	S										

FAT 65 Light Chain DNA and Amino Acid sequences

35 Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

FAT 66 Heavy Chain DNA Sequence SEQ ID NO. 157

GAGGTGCAGCTGGTGGAGACTGGGGAGGCCTGGTCCAGCCTGGGAGGTCCCTGAGACCC
 5 CCTGTGCAGCCTCTGGCTCATCTTCAGTGAECTGCTATACTACACTGGGTCCGCCAGGCTTC
 CGGGAAAGGGATGGAGTGGGTCTCATCCATTAGTAGTAGTAGTTACATATACTACGCA
 GACTCAGTGAAGGGCCGATTCAACCCTCAGAGACAACGCCAAGAACTCACTGTATTGCA
 AAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCCAGGAGGAAATAGT
 AGGGGACGGTATGGACGTCTGGGGCCGAGGGACCACGGTCACCGTCTCCTCT

10

FAT 66 Heavy Chain Amino Acid sequence SEQ ID NO. 158

E	V	Q	L	V	E	T	G	G	G	V	V	Q	P	G	R	S	L	R	P	S	
C	A	A	S	G	F	I	F	S	D	S	A	I	H	W	V	R	Q	A	S	G	
15	K	G	M	E	W	V	S	S	I	S	S	S	S	S	Y	I	Y	Y	A	D	S
V	K	G	R	F	T	I	S	R	D	N	A	K	N	S	L	Y	L	Q	M	N	
S	L	R	A	E	D	T	A	V	Y	Y	C	A	Q	E	G	I	V	G	D	G	
<u>M</u>	<u>D</u>	<u>V</u>	<u>W</u>	<u>G</u>	<u>R</u>	<u>G</u>	<u>T</u>	<u>T</u>	<u>V</u>	<u>T</u>	<u>V</u>	<u>S</u>	<u>S</u>								

20

FAT 66 Light Chain DNA and Amino Acid sequences

25 Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

FAT 67 Heavy Chain DNA Sequence SEQ ID NO. 159

GAGGTGCAGCTGGTGGAGTCTGGGGCTGAGGCGAAGAACGCCTGGGCCTCAGTGAAGGTCT
 30 CCTGCAAGGCTTCTGGTTCGCCTTACCAAACACTACGGTGTCAACTGGGTGCGACAGGCC
 AGGACAAAGGCTTGAGTGGATGGATGGATCAGCGCTCACGATGGTACACAAACTATGCA
 CAGAACCTCCGGGGCAGAGTCACCATGACCACAGACACATCCACGAGCACAGTCTACATGG
 ACCTGAGGGCCTGGAATCTGACGACACGGCGTATATTACTGTGCGAGTTGTGCGGGGTG
 TAGTGGTGGGATGATGCTTTGATATCTGGGCAAGGAAACCTGGTCACCGTCTCGTCT

35

49

FAT 67 Heavy Chain Amino Acid sequence SEQ ID NO. 160

E	V	Q	L	V	E	S	G	A	E	A	K	K	P	G	A	S	V	K	V	S	
C	K	A	S	G	S	A	F	T	N	Y	G	V	N	W	V	R	Q	A	P	G	
5	Q	R	L	E	W	M	G	W	I	S	A	H	D	G	D	T	N	Y	A	Q	N
L	R	G	R	V	T	M	T	T	D	T	S	T	S	T	V	Y	M	D	L	R	
G	L	E	S	D	D	T	A	V	Y	Y	C	A	S	C	A	G	C	S	G	G	
D	D	A	F	D	I	W	G	K	G	T	L	V	T	V	S	S					

10 FAT 67 Light Chain DNA and Amino Acid sequences

Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

15

FAT 68 Heavy Chain DNA Sequence SEQ ID NO. 161

CAGGTCCAGCTGGTGCAGTTGGGGAGGGCTGGTACAGCCAGGGCGGTCCCTGAGACGCT
 CCTGTGCAGCCTCTGGATTCACCTTAGCAGCTATGCCATGAGCTAGGTCCGCCAGGCTCC
 20 AGGGAAGGGCTGGAGTGGGTCTCAGCTATTAGTGGTAGTGGTGGTAGCACATACTACGCA
 GACTCCGTGAAGGGCCGGTCACCATCTCCAGAGACAATTCCAAGAACACGTTGTATCTGC
 AAATGGACAGCCTGAGAGCCGAGGACACGCCGTGTATTACTGTGCAAGATGCCAGTCGAT
 CAGCCATTGGGGCCGAGGCACCCTGGTCACCGTCTCCTCT

25 FAT 68 Heavy Chain Amino Acid sequence SEQ ID NO. 162

Q	V	Q	L	V	Q	F	G	G	G	L	V	Q	P	G	R	S	L	R	R	S	
C	A	A	S	G	F	T	F	S	S	Y	A	M	S	B	V	R	Q	A	P	G	
K	G	L	E	W	V	S	A	I	S	G	S	G	G	S	T	Y	Y	A	D	S	
30	V	K	G	R	F	T	I	S	R	D	N	S	K	N	T	L	Y	L	Q	M	D
S	L	R	A	E	D	T	A	V	Y	Y	C	A	R	C	O	S	I	S	H	W	
G	R	G	T	L	V	T	V	S	S												

FAT 68 Light Chain DNA and Amino Acid sequences

35

50

Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

FAT 69 Heavy Chain DNA Sequence SEQ ID NO. 163

5 CAGGTACATCTGAGGGAGTCTGGAGCAGAGGTGAAAAAGCCGGGGAGTCTCTGAAGATCT
 CATGTAAGGGTCTGGATACAGGGTTACCAACTACTGGATTGGCTGGTGCGCCAGATGCC
 CGGGAGAGGCCTGGAGTGGATGGGATCATCTATCCTGGTGA
 CCGTCCTCCAAGGCCAGGTCA
 CAGCCGACAAGTCATCAGCACCGCCTACCTGC
 AGTAGAGCAGCCTGAAGGCCTCGGACACCGCCATGTATTACTGTGCGAGACTGAGTGGCCA
 10 GCTGCTAATGGAGGATGCTTTGATATCTGGGCAAAGGGACAATGGTCACCGTCTTTCA

FAT 69 Heavy Chain Amino Acid sequence SEQ ID NO. 164

Q	V	I	L	R	E	S	G	A	E	V	K	K	P	G	E	S	L	K	I	S	
15	C	K	G	S	G	Y	R	V	T	N	Y	W	I	G	W	V	R	Q	M	P	G
	R	G	L	E	W	M	G	I	I	Y	P	G	D	S	D	T	R	Y	S	P	S
	F	Q	G	Q	V	T	I	S	A	D	K	S	I	S	T	A	Y	L	Q	B	S
	S	L	K	A	S	D	T	A	M	Y	Y	C	A	R	<u>L</u>	<u>S</u>	<u>G</u>	<u>Q</u>	<u>L</u>	<u>L</u>	<u>M</u>
20	E	D	A	F	<u>D</u>	<u>I</u>	W	G	K	G	T	M	V	T	V	S	S				

FAT 69 Light Chain DNA and Amino Acid sequences

Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

FAT 71 Heavy Chain DNA Sequence SEQ ID NO. 165

5 CAGGTACACCTTGAAGGAGTCTGGGCTGAGGTGAAGAAGCCTGGGCCTCAGTGAAGGTCT
 CCTGCAAGGTTACCGGGACCAACCTCAGTGAATTATCCATCCACTGGCGCGACAGGCTCC
 CGGAAAGGGCTGAGTGGATGGAGGTTTGATCCTGAAGATGTGCAAATAGCCTACGCC
 30 CAGGAGTTCCAGGGCGGACTGCCATGACCGAGGACACATCCATAGACACAGCCCACATGG
 AGCTGAGTAGCCTGAGATCTGAGGACACGGCCGTGTATTTGTGTAGCAGGGGGACTCC
 GGTGGTCCACGATGATGCTTTGAAATTGGGCCAGAGGACAATGGTCACCGTGTCTCA

51

FAT 71 Heavy Chain Amino Acid sequence SEQ ID NO. 166

Q	V	T	L	K	E	S	G	A	E	V	K	K	P	G	A	S	V	K	V	S	
C	K	V	T	G	T	N	L	S	E	L	S	I	H	W	A	R	Q	A	P	G	
5	K	G	L	E	W	M	G	G	F	D	P	E	D	V	Q	I	A	Y	A	Q	E
F	Q	G	G	L	A	M	T	E	D	T	S	I	D	T	A	H	M	E	L	S	
S	L	R	S	E	D	T	A	V	Y	F	C	V	A	<u>G</u>	<u>G</u>	T	P	V	V	H	
D	D	A	F	E	I	W	G	Q	R	T	M	V	T	V	S	S					

10 FAT 71 Light Chain DNA and Amino Acid sequences

Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

FAT 72 Heavy Chain DNA Sequence SEQ ID NO. 167

15	CAGGTACAGCTGCAGCAGTCAGGAGCAGAGGTGAAAAGGCCGGGAATCTCTGAAGATCT																			
	CCTGTCAGGGTTCTGGATACAGCTTCCCAACTCTGGCTCGCCTGGGTGCGCCAGACGCC																			
	CGGGAAAGACCTGGAGTGGATGGCCATCATCAATCCCGGAAATTCTGATACCAGATACAGC																			
	CCGTCTTCCAAGGGCAGGTACCACATACCGCCGACAACCTATCAGCACCATGTTCTGC																			
20	ACTAGAACAGCCTGAAGGCCTGGACACCGCCTTGTATTACTGTGCGAGAGCTGGGTCGC																			
	GGGCGGTGCTCTGATCTGGGCCAAGGAACTCTGGTCACCGTCTCCAGT																			

FAT 72 Heavy Chain Amino Acid sequence SEQ ID NO. 168

25	Q	V	Q	L	Q	Q	S	G	A	E	V	K	R	P	G	E	S	L	K	I	S
	C	Q	G	S	G	Y	S	F	P	N	S	W	L	A	W	V	R	Q	T	P	G
	K	D	L	E	W	M	A	I	I	N	P	G	N	S	D	T	R	Y	S	P	S
	F	Q	G	Q	V	T	I	T	A	D	N	S	I	S	T	M	F	L	H	B	N
	S	L	K	A	S	D	T	A	L	Y	Y	C	A	R	<u>A</u>	<u>G</u>	V	A	G	G	A
30	<u>S</u>	<u>D</u>	<u>L</u>	W	G	Q	G	T	L	V	T	V	S	S							

FAT 72 Light Chain DNA Sequence SEQ ID NO. 169

35	CAGTCTGTGTTGACGCAGCCGCCCTCAGTGTCTGCGGCCAGGACAGAAGGTCACCATT																			
	CCTGCTCTGGAAGCACCTAACATTGGGATAATTATGTCACCTGGTACCAACAGCACCC																			

AGGCAAAGCCCACAAACTCATGATTTATGATGTCAGTAAGCGGCCCTCAGGGGTCCCTGAC
 CGATTCTCTGGCTCCAAGTCTGGCAACTCAGCCTCCCTGGACATCAGTGGCTCCAGTCTG
 AGGATGAGGCTGATTATTACTGTGCAGCATGGATGACAGCCTGAGTGAATTCTCTTCGG
 AACTGGGACCAAGCTGACCGTCGTAGGT

5

FAT 72 Light Chain Amino Acid sequence SEQ ID NO. 170

Q	S	V	L	T	Q	P	P	S	V	S	A	A	P	G	Q	K	V	T	I	S	
C	S	G	S	T	S	N	I	G	N	N	Y	V	T	W	Y	Q	Q	H	P	G	
10	K	A	H	K	L	M	I	Y	D	V	S	K	R	P	S	G	V	P	D	R	F
	S	G	S	K	S	G	N	S	A	S	L	D	I	S	G	L	Q	S	E	D	E
	A	D	Y	Y	C	A	A	W	D	D	S	L	S	E	F	L	F	G	T	G	T
	K	L	T	V	V	G															

15 FAT 73 Heavy Chain DNA Sequence SEQ ID NO. 171

CAGGTACAGCTGCAGCAGTCAGGAGCAGAGGTGAAGAAGCCGGGGAGTCTCTGAGGATCT
 CCTGTAAGGTTCAAGGATACAACCTTAACACCTATTGGATCGGCTAGGTGCGCCAGGTGCC
 CGGGAAAGGCCTGGAGTGGATGGAATCATCTATCCTCGTACTCTAATACCAGATATAGC
 20 CCGTCCTTCCAAGGCCAGGTACCATGTCAGTCAGACAAGTACGCCAACACCGCCTACTTAC
 AGTGGAGCAGCCTGAAGGCCTCGGACACCGCCATGTATTACTGCGCGAAGCATAATATGAT
 TGCTCGTCCATATGATCCTTTGATATCTGGGGCAAGGGCACCCCTGGTCACCGTCTCGAGT

FAT 73 Heavy Chain Amino Acid sequence SEQ ID NO. 172

25	Q	V	Q	L	Q	Q	S	G	A	E	V	K	K	P	G	E	S	L	R	I	S	
	C	K	G	S	G	Y	N	F	N	T	Y	W	I	G	B	V	R	Q	V	P	G	
	K	G	L	E	W	M	G	I	I	Y	P	R	D	S	N	T	R	Y	S	P	S	
	F	Q	G	Q	V	T	M	S	V	D	K	Y	A	N	T	A	Y	L	Q	W	S	
30	S	L	K	A	S	D	T	A	M	Y	Y	C	A	K	<u>H</u>	<u>N</u>	<u>M</u>	<u>I</u>	<u>A</u>	<u>R</u>	<u>P</u>	
	<u>Y</u>	<u>D</u>	<u>P</u>	<u>F</u>	<u>D</u>	<u>I</u>	<u>W</u>	<u>G</u>	<u>K</u>	<u>G</u>	<u>T</u>	<u>L</u>	<u>V</u>	<u>T</u>	<u>V</u>	<u>S</u>	<u>S</u>					

FAT 73 Light Chain DNA and Amino Acid sequences

35 Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

FAT 74 Heavy Chain DNA Sequence SEQ ID NO. 173

GGGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGCCTCAGTGAAGGTCT
 5 CCTGCAAGGCTTCTGGATAACACCTCACCGGCTACTATATACTGGGTGCGACAGGCC
 TGGACAAGGGCTTGAGTGGATGGGAGGAATCATCCCTATCTTGGTACAACATACTACGCA
 CAGAATTCCAGGACAGACTGTCATTACCGCGAACGAACTCCACGAGCACAGCCTACATGG
 AACTGAGCCGCCTGAGATCTGGGACACGCCATGTATTACTGTGCGAGAGATGGTCAGGG
 GCGTGGCTGGGACGTGACTGGTATTCGATATCTGGGCCAGGGACAATGGTCACCGTC
 10 TCGA

15 FAT 74 Heavy Chain Amino Acid sequence SEQ ID NO. 174

G	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	A	S	V	K	V	S	
C	K	A	S	G	Y	T	F	T	G	Y	Y	I	H	W	V	R	Q	A	P	G	
Q	G	L	E	W	M	G	G	I	I	P	I	F	G	T	T	Y	Y	A	Q	N	
20	F	Q	D	R	L	S	I	T	A	D	E	S	T	S	T	A	Y	M	E	L	S
R	L	R	S	G	D	T	A	M	Y	Y	C	A	R	<u>D</u>	<u>G</u>	<u>Q</u>	<u>G</u>	<u>R</u>	<u>G</u>	<u>W</u>	
G	R	D	W	Y	F	D	<u>I</u>	W	G	R	G	T	M	V	T	V	S				

FAT 74 Light Chain DNA Sequence SEQ ID NO. 175

25 GACATCGTATGACCCAGTCTCCTTCCACCTGTCTGCATCTGTAGGAGACAGAGTCACCA
 TCACTTGCCGGGCCAGTCAGGGTATTAGTAGCTGGTGGCCTGGTATCAGCAGAAACCAGG
 GAGAGCCCCTAACGGTCTTGATCTATAAGGCATCTACTTAGAAAGTGGGGTCCCATCAAGG
 TTCAGCGGCAGTGGATCTGGACAGATTCACTCTCACCATCAGCAGTCTGCAACCTGAAG
 30 ATTTTGCAACTTACTACTGTCAACAGAGTTACAGTACCCCGTGGACGTTGGCCAAGGGAC
 CAAGCTGGAGATCAAACGTGCGGCC

FAT 74 Light Chain Amino Acid Sequence SEQ ID NO. 176

54

D	I	V	M	T	Q	S	P	S	T	L	S	A	S	V	G	D	R	V	T	I	
T	C	R	A	S	Q	G	I	S	S	W	L	A	W	Y	Q	Q	K	P	G	R	
A	P	K	V	L	I	Y	K	A	S	T	L	E	S	G	V	P	S	R	F	S	
G	S	G	S	G	T	D	F	T	L	T	I	S	S	L	Q	P	E	D	F	A	
5	T	Y	Y	C	Q	Q	S	Y	S	T	P	W	T	F	G	Q	G	T	K	L	E
	I	K	R	A	A																

FAT 75 Heavy Chain DNA sequence SEQ ID NO. 177

10

CAGGTGCAGCTACAGCTGTAGGGCGCTGGACTGTTGAAGCCTTCGGAGACCCTGTCCCTCA
 CTTGCGCTGTCTATGGTGGGTCTTCATGCTGATCACTGGAGCTGGATCCGCCAGCCCC
 AGAGAAGGGGCTAGAGTGGGTCTCAGCTATTAGTGGTAGTGGTGGTAGCACATACTACGCA
 GACTCCGTGAAGGGCCGGTTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGC
 15 AAATGAACAGCCTGAGAGCCGAGGACACGCCGTATATTACTGTGCGAAAGATCTGATATC
 CCCGTACTACTACTACGGTATGGACGTCTGGGCCAGGGCACCCCTGGTCACCGTCTCCTCA

FAT 75 Heavy Chain Amino Acid sequence SEQ ID NO. 178

20

Q	V	Q	L	Q	L	B	G	A	G	L	L	K	P	S	E	T	L	S	L	T
C	A	V	Y	G	G	S	F	N	A	D	H	W	S	W	I	R	Q	P	P	E
K	G	L	E	W	V	S	A	I	S	G	S	G	G	S	T	Y	Y	A	D	S
V	K	G	R	F	T	I	S	R	D	N	S	K	N	T	L	Y	L	Q	M	N
S	L	R	A	E	D	T	A	V	Y	Y	C	A	K	<u>D</u>	<u>L</u>	<u>I</u>	<u>S</u>	<u>P</u>	<u>Y</u>	<u>Y</u>
25	Y	Y	G	M	D	V	W	G	Q	G	T	L	V	T	V	S	S			

FAT 75 Light Chain DNA and Amino Acid sequences

Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

30

FAT 76 Heavy Chain DNA sequence SEQ ID NO. 179

CAGGTGCAGCTGCAGGAGTCGGGGCTGAGGTGAAGAAGCCTGGTCCTCGGTGAAGGTCT
 CCTGCAAGGCTTCTGGAGGCACCTTCAGCAGGTATGCTATCAGCTAGGTGCGACAGGCC
 35 TGGACAAGGGTTGAGTGGATGGATCAGCGCTTACAATGGTGACACAAACTATGCA

CAGAACCTCCAGGGCAGAGTCACCATGACCACAGACACATCCACGACCACAGCCTACATGG
 AGCTGAGGAGCCTGAGATCTGACGACACGGCCGTGTATTACTGTGCGAGAGGGGGGGTAT
 TCGCGGTATGGACGCCTGGGGAGAGGACCACGTCACGTGTCGAGT

5 FAT 76 Heavy Chain Amino Acid sequence SEQ ID NO. 180

Q	V	Q	L	Q	E	S	G	A	E	V	K	K	P	G	S	S	V	K	V	S	
C	K	A	S	G	G	T	F	S	R	Y	A	I	I	S	B	V	R	Q	A	P	G
Q	G	L	E	W	M	G	W	I	S	A	Y	N	G	D	T	N	Y	A	Q	N	
10	L	Q	G	R	V	T	M	T	T	D	T	S	T	T	T	A	Y	M	E	L	R
	S	L	R	S	D	D	T	A	V	Y	Y	C	A	R	<u>G</u>	<u>G</u>	<u>G</u>	<u>I</u>	<u>R</u>	<u>G</u>	<u>M</u>
	<u>D</u>	<u>A</u>	W	G	R	G	P	R	H	V	S	S									

FAT 76 Light Chain DNA and Amino Acid sequences

15 Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

FAT 77 Heavy Chain DNA Sequence SEQ ID NO. 181

20 CAGGTGCAGCTGCAGGAGTCCGGGGAGGCTTGGTACGGCCTGGCAGGTCCCTGAGACTCT
 CCTGTGCAGCCTCTGGATTACACCTTGTATGATTATGCCATGCACGGTCCGGCAAGCTCC
 AGGGAAGGGCCTGGAGTGGGTCTCAGGTATTAGTTGGAATAGTGGTAGCATAGGCTATGCG
 GACTCTGTGAAGGGCCGATTACCATCTCAGAGACAACGCCAAGAACTCCCTGTATCTGC
 AAATGAACAGTCTGAGAGCTGAGGACACGGCCTTGTATTACTGTGCAAAGGAACAGGCCGA
 25 CGGTCCCGGTATAGCAGTGGCTGGTACGGGCTACATGGACGTCTGGGGAGGGACAATGG
 TCACCTGTCTTCAGGTGGAGGGAGTTCAA

30 FAT 77 Heavy Chain Amino Acid sequence SEQ ID NO. 182

Q	V	Q	L	Q	E	S	G	G	G	L	V	R	P	G	R	S	L	R	L	S	
C	A	A	S	G	F	T	F	D	D	Y	A	M	H	W	V	R	Q	A	P	G	
K	G	L	E	W	V	S	G	I	S	W	N	S	G	S	I	G	Y	A	D	S	
35	V	K	G	R	F	T	I	S	R	D	N	A	K	N	S	L	Y	L	Q	M	N

56

S	L	R	A	E	D	T	A	L	Y	Y	C	A	K	<u>E</u>	<u>Q</u>	<u>A</u>	<u>D</u>	<u>G</u>	<u>P</u>	<u>R</u>
<u>I</u>	<u>A</u>	<u>V</u>	<u>A</u>	<u>G</u>	<u>T</u>	<u>G</u>	<u>Y</u>	<u>M</u>	<u>D</u>	<u>V</u>	<u>W</u>	<u>G</u>	<u>R</u>	<u>G</u>	<u>Q</u>	<u>W</u>	<u>S</u>	<u>P</u>	<u>V</u>	<u>F</u>
R	W	R	S	S																

5 FAT 77 Light Chain DNA and Amino Acid sequences

Identical to FAT 31 (SEQ ID NO.'s 87 and 88)

10 FAT 78 Heavy Chain DNA Sequence SEQ ID NO. 183

CAGGTGCAGCTGTAGGAGTCGGGGGGAGGCTTGGTGCAGCCTGGAAGGTCTCTGAGACTCT
 CCTGTGCAGCCTCTGGATTCAAGCTTGATGACTACGGCATGCACGGTCCGGCAAGCTCC
 AGGGAAGGGCCTGGAGTGGGTCTCAGGTATTAGTTGGAATAGTGGTAGCATAGGCTATGCG
 GACTCTGTGAAGGGCCGATTCAACCCTCAGAGACAACGCCAAGAACTCCCTGTATCTGC
 15 AAATGAACAGTCTGAGAGCTGAGGACACGGCCTTGTATTACTGTGTGAAAGCTGGACGGGG
 GGACTACTGGGCCGGACCACGGTCACCGTCTCCTCA

15 FAT 78 Heavy Chain Amino Acid sequence SEQ ID NO. 184

20	Q	V	Q	L	B	E	S	G	G	G	L	V	Q	P	G	R	S	L	R	L	S
	C	A	A	S	G	F	S	F	D	D	Y	G	M	H	W	V	R	Q	A	P	G
	K	G	L	E	W	V	S	G	I	S	W	N	S	G	S	I	G	Y	A	D	S
	V	K	G	R	F	T	I	S	R	D	N	A	K	N	S	L	Y	L	Q	M	N
	S	L	R	A	E	D	T	A	L	Y	Y	C	V	K	<u>A</u>	<u>G</u>	<u>R</u>	<u>G</u>	<u>D</u>	<u>Y</u>	<u>W</u>
25	G	R	T	T	V	T	V	S	S												

20 FAT 78 Light Chain DNA and Amino Acid sequences

Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

30 FAT 79 Heavy Chain DNA Sequence SEQ ID NO. 185

CAGGTGCAGCTGGTGGAGTCTGGGGAGGCTTGGTACAGCCTGGCAGGTCCCTGAGACTCT
 CCTGTGCAGCCTCTGGATTCAACCTTGATGATTATGCCATGCACGGTCCGGCAAGCTCC
 35 AGGGAAGGGCCTGGAGTGGGTCTCAGGTATTAGTTGGAATAGTGGTAGCATAGGCTATGCG

GA
CTCTGTGAAGGGCCGATTCA
CCATCTCCAGAGACA
ACGCCAAGAA
CTCC
GTATCTGC
AA
ATGAACAGCCTGAGAGCTGAGGACACGGCCGTATATTACTGTG
CGAAAGATCGAAGGAC
ACTCGACTACTTGACTACTGGGCCGGGCAATGTCACC
GTCTTCA

5 FAT 79 Heavy Chain Amino Acid sequence SEQ ID NO. 186

Q	V	Q	L	V	E	S	G	G	G	L	V	Q	P	G	R	S	L	R	L	S	
C	A	A	S	G	F	T	F	D	D	Y	A	M	H	W	V	R	Q	A	P	G	
K	G	L	E	W	V	S	G	I	S	W	N	S	G	S	I	G	Y	A	D	S	
10	V	K	G	R	F	T	I	S	R	D	N	A	K	N	S	L	Y	L	Q	M	N
	S	L	R	A	E	D	T	A	V	Y	Y	C	A	K	<u>D</u>	<u>R</u>	<u>R</u>	<u>T</u>	<u>L</u>	<u>D</u>	<u>Y</u>
	<u>F</u>	<u>D</u>	<u>Y</u>	<u>W</u>	<u>A</u>	<u>G</u>	<u>A</u>	<u>N</u>	<u>V</u>	<u>T</u>	<u>V</u>	<u>S</u>	<u>S</u>								

15

FAT 79 Light Chain DNA and Amino Acid sequences

Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

20 FAT 82 Heavy Chain DNA Sequence SEQ ID NO. 187

GAGGTGCAGCTGGTGGAGTCTGGGGAGGC
GTGGTCCAGCCTGGG
CTGGGAGCTCCCTGAGACTCT
CCTGTGCAGCCTCTGGATT
CACCTCAGTC
ACTGGTCC
TACGACATA
CAACTGGTCCGCCAAGCTAC
AGGAAAAGGTCTGG
AATGGGTCTCAGGTATTGGTACTG
CTGGTGACCC
ATACTATCCAGGC
25 TCCGTGAAGGGCCGATT
CACCATCTCCAGAGACA
ACGCCAAGAA
CTCACTGTATCTG
CAAATGAACAGC
CTGAGAGCC
GAGGACACGG
CTGTATTACTG
TGC
GAGATCT
CCCCCAGTA
TTACTATG
ACAGTAGTGG
ATATTACTAC
CCCTGAATA
CTTCCAGC
ACTGGGGCC
GGGGCACC
CTGGTCACCGT
GTCGAGT

30 FAT 82 Heavy Chain Amino Acid sequence SEQ ID NO. 188

E	V	Q	L	V	E	S	G	G	G	V	V	Q	P	G	G	S	L	R	L	S	
C	A	A	S	G	F	T	F	S	S	Y	D	I	H	W	V	R	Q	A	T	G	
K	G	L	E	W	V	S	G	I	G	T	A	G	D	P	Y	Y	P	G	S	V	
35	K	G	R	F	T	I	S	R	D	N	A	K	N	S	L	Y	L	Q	M	N	S

58

L	R	A	E	D	T	A	V	Y	Y	C	A	R	<u>D</u>	<u>L</u>	<u>P</u>	<u>Q</u>	<u>Y</u>	<u>Y</u>	<u>Y</u>	<u>D</u>
S	S	G	Y	Y	Y	P	E	Y	F	Q	H	W	G	R	G	T	L	V	T	V
S	S																			

5 FAT 82 Light Chain DNA and Amino Acid sequences

Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

10 FAT 84 Heavy Chain DNA Sequence SEQ ID NO. 189

CAGGTGCAGCTGGTGCAATCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCT
 CCTGTGCAGCCTCTGGATTCACCTCAGTAGCTATGGCATGCAGTGGGTCCGCCAGGCTCC
 AGGCAAGGGGCTGGAGTGGGTGGCAGTTATCATATGATGGAAGTATTAAATACTATGCA
 GACTCCGTGAAGGGCCGATTCAACCCTCAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAAAGGCTATGGGAG
 15 AAATGAACAAACCTCAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAAAGGCTATGGGAG
 TTCTTACGGGGAACTTCCTGGGCCAGGGAACCCCTGGTCACACGTTCTTCC

15 FAT 84 Heavy Chain Amino Acid sequence SEQ ID NO. 190

20 Q V Q L V Q S G G G V V Q P G R S L R L S
 C A A S G F T F S S Y G M H W V R Q A P G
 K G L E W V A V I S Y D G S I K Y Y A D S
 V K G R F T I S R D N S K N T L Y L Q M N
 N L R A E D T A V Y Y C A K G Y G S S Y G
 25 G T S W A Q G T L V T R S S

20 FAT 84 Light Chain DNA and Amino Acid sequences

Identical to FAT 7 (SEQ ID NO.'s 25 and 26)

30

FAT 86 Heavy Chain DNA Sequence SEQ ID NO. 191

CAGGTACAGCTGCAGCAGTCAGGGGGAGGCTTGGTTCAGCCTGGCAGGTCCCTGAGACTCT
 CCTGCGTAGTCTGGATCTACGTATGTCGGCCCAGCCATACACTGGGTCCGGCAAGCTCC
 35 AGGGAAGGGCCTGGAATACGTCGAGGTATTGGTTGGAGTAGTGATACGAAAGGCTATGCG

GAACCTGTGAGGGGCCAATTACCATCTCCAGAGACAACGCCAAGAACGCCCTGTATCTGC
 AAATGAACAGTCTGAGACCTGAGGACACGGCTGTGTATCACTGTGCGAAGCAATATAGTGG
 CTACGATTATTGGGACTACTTTGACTACTGGGGCAGGGACCACGGTCACCGTCTCGAGT

5 FAT 86 Heavy Chain Amino Acid sequence SEQ ID NO. 192

Q	V	Q	L	Q	Q	S	G	G	G	L	V	Q	P	G	R	S	L	R	L	S	
C	V	V	S	G	S	T	Y	V	G	P	A	I	H	W	V	R	Q	A	P	G	
K	G	L	E	Y	V	A	G	I	G	W	S	S	D	T	K	G	Y	A	D	S	
10	V	R	G	Q	F	T	I	S	R	D	N	A	K	N	A	L	Y	L	Q	M	N
	S	L	R	P	E	D	T	A	V	Y	H	C	A	K	Q	Y	S	G	Y	D	Y
	W	D	Y	F	D	Y	W	G	Q	G	T	T	V	T	V	S	S				

FAT 86 Light Chain DNA and Amino Acid sequences

15 Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

FAT 87 Heavy Chain DNA Sequence SEQ ID NO. 193

20 CAGGTGCAGCTGGTGCAGTCTGGGGAGGCCTGGTCAAGCCTGGGGTCCCTGAGACTCT
 CCTGTGAAGTCTCTGGATTGAGGTTCAGCAGCTACGGCATGAATTGGGTCCGCCAGGCTCC
 AGGGAAGGCACTGGAGTGGGTCTCATCCATAGCAACCACTGAAAGATTCACATCGTACGCA
 GACTCAGTGAAGGGCCGATTCTCCATCTCAGAGACGACGCCAAGAACTCAGTTATCTGC
 AGATGGACAGCCTGAGGGCGAGGACACGCCGTATATTACTGTGCGAAGTCGAAGGTAGG
 25 GGGTGGCAATGACTACTGGGCAGAGGGACAATGGTCACCGTCTCCTCA

30 FAT 87 Heavy Chain Amino Acid sequence SEQ ID NO. 194

Q	V	Q	L	V	Q	S	G	G	G	L	V	K	P	G	G	S	L	R	L	S	
C	E	V	S	G	L	R	F	S	S	Y	G	M	N	W	V	R	Q	A	P	G	
K	A	L	E	W	V	S	S	I	A	T	T	E	R	F	T	S	Y	A	D	S	
35	V	K	G	R	F	S	I	S	R	D	D	A	K	N	S	V	Y	L	Q	M	D

60

S	L	R	A	E	D	T	A	V	Y	Y	C	A	K	S	K	V	G	G	G	N
<u>D</u>	<u>Y</u>	W	G	R	G	T	M	V	T	V	S	S								

FAT 87 Light Chain DNA and Amino Acid sequences

5

Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

FAT 88 Heavy Chain DNA Sequence SEQ ID NO. 195

10	GAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTCT
	CCTGCAAGGCTTCTGGAGGCACCTTAGCAGATATGCTATCAGCTGGGTGCGACAGGCC
	TGGACAAGGGCTTGAGTGGATGGGAGGGATCATCCCTTCATGGTACAGCAAACATACGCA
	CAGAGGTTCCAGGGCAGAGTCACCATGACCACAGACACATCCACGAGCACAGCCTACATGG
15	AGCCGAGGAGCCTGAGATCTGACGACACGCCGTGTATTACTGTGCGAGAGATTATAGCAG
	CAGACGGTACAGCTACTTGACTACTAGGCCAGGGAACCTGGTCACAGTGTCCCTCA

FAT 88 Heavy Chain Amino Acid sequence SEQ ID NO. 196

E	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	A	S	V	K	V	S	
20	C	K	A	S	G	G	T	F	S	R	Y	A	I	S	W	V	R	Q	A	P	G
	Q	G	L	E	W	M	G	G	I	I	P	S	Y	G	T	A	N	Y	A	Q	R
	F	Q	G	R	V	T	M	T	T	D	T	S	T	S	T	A	Y	M	E	P	R
	S	L	R	S	D	D	T	A	V	Y	Y	C	A	R	<u>D</u>	<u>Y</u>	<u>S</u>	<u>S</u>	<u>R</u>	<u>R</u>	<u>Y</u>
	<u>S</u>	<u>Y</u>	<u>F</u>	<u>D</u>	<u>Y</u>	B	G	Q	G	T	L	V	T	V	S	S					

25

FAT 88 Light Chain DNA and Amino Acid sequences

Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

30 FAT 89 Heavy Chain DNA Sequence SEQ ID NO. 197

10	CAGGTGCAGCTGCAGGAGTCGGGCCAGGACTGGTGAAGCCTCGGGGACCCGTCCCTCA
	CCTGCGCTGTCTGGTGCCTCCATCAGCAATGGTTCTGGTGGGCTGGGTACGCCAGCC
	CCCAGGGAGGGTCTGGAGTGGATTGGGAAATCTTTTACTGGACGCGCCAATTACAAC
35	CCGTCCCTGAAGAGTCGAGTCACCACATCAGTAGACGAGTCCAAGAACAGTTCTCCCTGA

61

AGTTGACCTCTGTGACGCCGCGGACACGGCCGTATATTCTGTGCGAGAGACCGGGACAC
TGGCTAGTACTTCTTGACGACTGGGGCAAAGGGACAATGGTCACCGTCTCGAGT

FAT 89 Heavy Chain Amino Acid sequence SEQ ID NO. 198

5

Q	V	Q	L	Q	E	S	G	P	G	L	V	K	P	S	G	T	L	S	L	T	
C	A	V	S	G	A	S	I	S	N	G	F	W	W	G	W	V	R	Q	P	P	
G	R	G	L	E	W	I	G	E	I	F	F	T	G	R	A	N	Y	N	P	S	
L	K	S	R	V	T	T	S	V	D	E	S	K	N	Q	F	S	L	K	L	T	
10	S	V	T	A	A	D	T	A	V	Y	F	C	A	R	<u>D</u>	<u>R</u>	<u>D</u>	<u>T</u>	<u>G</u>	<u>B</u>	<u>Y</u>
	<u>F</u>	<u>F</u>	<u>D</u>	<u>D</u>	W	G	K	G	T	M	V	T	V	S	S						

FAT 89 Light Chain DNA and Amino Acid sequences

15 Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

FAT 90 Heavy Chain DNA sequence SEQ ID NO. 199

20 GAGGTGCAGCTGGTGGAGACCGGGGGAGGCTTGGTACAGCCTGGCAGGTCCGTGAGACTCT
CCTGTGCAGCCTCTGGATTCACCTTGATGATTATGCCATGCACGGCTCCGGAACCTCC
AGGGAAGGGCCTGGAGTAGGTCTCAACTATTAGTGGTAGTGGTGGTAGCACGTACTACGCA
GAECTCGTGAAGGGCCGGATCACCATCTCCAGAGACAATTCCAAGAACACGCCGTATCTGC
AAATGAACAGCCTGAGAGTCGGGGACACGGCCGCATATTACTGTGCGAAAGACCCCTATTG
TGGTAGTGCCAGCTGCTATACTTATCATGCTTTGATCTGGGGCCAAGGCACCCCTGGTC
25 ACCGTCTCGAGT

FAT 90 Heavy Chain Amino Acid sequence SEQ ID NO. 200

E	V	Q	L	V	E	T	G	G	G	L	V	Q	P	G	R	S	V	R	L	S	
30	C	A	A	S	G	F	T	F	D	D	Y	A	M	H	W	L	R	Q	P	P	G
	K	G	L	E	B	V	S	T	I	S	G	S	G	G	S	T	Y	Y	A	D	S
	V	K	G	R	I	T	I	S	R	D	N	S	K	N	T	P	Y	L	Q	M	N
	S	L	R	V	G	D	T	A	A	Y	Y	C	A	K	<u>D</u>	<u>P</u>	<u>Y</u>	<u>C</u>	<u>G</u>	<u>S</u>	<u>A</u>
	<u>S</u>	<u>C</u>	<u>Y</u>	<u>T</u>	<u>Y</u>	<u>H</u>	<u>A</u>	<u>F</u>	<u>D</u>	<u>L</u>	<u>W</u>	<u>G</u>	<u>Q</u>	<u>G</u>	<u>T</u>	<u>L</u>	<u>V</u>	<u>T</u>	<u>V</u>	<u>S</u>	<u>S</u>

FAT 90 Light Chain DNA and Amino Acid sequences

Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

5 FAT 91 Heavy Chain DNA Sequence SEQ ID NO. 201

CAGGTGCAGCTGCAGGAGTCGGGGGAGGCTTGGTACAGCCTGGCAGGTCCCTGAGACTCT
 CCTGTGCAGCCTCTGGATTCAAGGTTGATGATTATGCCATGCACTAGGTCCGGCAAGCTCC
 AGGGAAGGGCCTGGAGTGGGTGCGCTGGTATTGATTGGAATAGTGGTTCCATCGGCTATGTG
 10 GACTCTGTGAAGGGCCGATTCACCCCTCTCCAGAGACAACGCCAAGAACTCCCTGTATCTGC
 AAATGAACAGTCTGAGAGCTGAGGACACGGCCTTGTATTACTGTGAAAAGACAAAGAGTA
 TAGCAGCTCGTACTACTTGACTACTGGGCCGGGACAATGGTCACAGTTCTGCTTC

FAT 91 Heavy Chain Amino Acid sequence SEQ ID NO. 202

15 Q V Q L Q E S G G G L V Q P G R S L R L S
 C A A S G F R F D D Y A M H B V R Q A P G
 K G L E W V A G I D W N S G S I G Y V D S
 V K G R F T L S R D N A K N S L Y L Q M N
 20 S L R A E D T A L Y Y C A K D K E Y S S S
 Y Y F D Y W G R G Q W F T V L L

FAT 91 Light Chain DNA and Amino Acid sequences

25 Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

FAT 92 Heavy Chain DNA sequence SEQ ID NO. 203

GAGGTGCAGCTGGTGCAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCGTGCGACTCT
 30 CCTGTGCAGCCTCTGGATTCAACCTTCAGTACTCATGGCATGCACACTGGTCCGCCAGGCTCC
 AGGCAAGGGGCCGGAGTGGCTGACATTTATCTCATATGATGAGAGTGAAAAATCTTATGCA
 GACTCCGTGAAGGGCCGATTACCCATCTCAGAGACAATTCCGAGAAAACACTGTATCTGC
 AAATGAACAGTCTGAGACCTGAGGACACGGCTGTGTATTACTGTGCGAAAGATGTCTTGAT
 ACACCAAACGTACAAGTGGTCGACCCCTGGGCAAGGGCACCTGGTCACCGTCTCCTCA

FAT 92 Heavy Chain Amino Acid sequence SEQ ID NO. 204

5	E	V	Q	L	V	Q	S	G	G	G	V	V	Q	P	G	R	S	L	R	L	S
	C	A	A	S	G	F	T	F	S	T	H	G	M	H	W	V	R	Q	A	P	G
	K	G	P	E	W	L	T	F	I	S	Y	D	E	S	E	K	S	Y	A	D	S
	V	K	G	R	F	T	I	S	R	D	N	S	E	K	T	L	Y	L	Q	M	N
	S	L	R	P	E	D	T	A	V	Y	Y	C	A	K	<u>D</u>	V	L	I	H	Q	T
10	<u>Y</u>	K	W	F	D	P	W	G	K	G	T	L	V	T	V	S	S				

FAT 92 Light Chain DNA and Amino Acid sequences

Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

15

FAT 93 Heavy Chain DNA sequence SEQ ID NO. 205

	CAGGTGCAGCTGGTGGAGTCTGGGGAGGCTGGTACAGCCTGGAGGGTCCCTGAGACTCC
	CCTGTGCAGCCTCTGGATTACACCTTCAGTAGTTATGAAATGAACTGGGTCCGCCAGGCTCC
20	AGGGAGGGGGCGGGAGTGGGTCTCGGTATTAATTGGAATGGTGGTAACACAGGTTATGCG
	GACTCTGTGAAGGGCCGATTACCATCTCCCGAGACAACGCCAGGAACACTCCGTATCTGC
	AAATGAACAGTCCGAGAGCCGAGGACACGGCCTGTATTCTGTGTGAGAGATCGGAATCA
	ATACTATGATAGTGGTGGTTATCCTGATTCTTGATATCTGGGCCAGTGGACAATGGTC
	ACAGTCTCTTCA

25

FAT 93 Heavy Chain Amino Acid sequence SEQ ID NO. 206

	Q	V	Q	L	V	E	S	G	G	G	L	V	Q	P	G	G	S	L	R	L	P
	C	A	A	S	G	F	T	F	S	S	Y	E	M	N	W	V	R	Q	A	P	G
30	R	G	R	E	W	V	S	G	I	N	W	N	G	G	N	T	G	Y	A	D	S
	V	K	G	R	F	T	I	S	R	D	N	A	R	N	S	L	Y	L	Q	M	N
	S	P	R	A	E	D	T	A	L	Y	S	C	V	R	<u>D</u>	R	N	Q	Y	Y	D
	<u>S</u>	G	G	Y	P	D	S	F	D	I	W	G	Q	W	T	M	V	T	V	S	S

35 FAT 93 Light Chain DNA and Amino Acid sequences

Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

FAT 94 Heavy Chain DNA sequence SEQ ID NO. 207

5 GAGGTGCAGCTGGTGGAGACCGGGGGAGGCCTGGTCAAGCCTGGGGGTCCCTGAGACTCT
 CCTGTGCAGCCTCTGGATTCACCTCAGTGACTACTGCATGAGCTGGATCCGCCAGGCTCC
 AGGGAAGGGGCTGGAGTGGGTTCCATACATTAGTAGTAGTAGTACCATATACTACGCA
 GACTCTGTGAAGGGCCGATTCAACCATCTCCAGAGACAATGCCAAGAACTCACTGTATCTAC
 AAATGAACAGCCTGAGAGCCGAGGACACGGCTGTCTATTACTGTGCGAGACTTGGTACCGA
 10 GACTATTGACTATTGGGGCGGGGACCACTGTCACCGTCTCGAGTT

FAT 94 Heavy Chain Amino Acid sequence SEQ ID NO. 208

	E	V	Q	L	V	E	T	G	G	L	V	K	P	G	G	S	L	R	L	S	
15	C	A	A	S	G	F	T	F	S	D	Y	C	M	S	W	I	R	Q	A	P	G
	K	G	L	E	W	V	P	Y	I	S	S	S	S	S	T	I	Y	Y	A	D	S
	V	K	G	R	F	T	I	S	R	D	N	A	K	N	S	L	Y	L	Q	M	N
	S	L	R	A	E	D	T	A	V	Y	Y	C	A	R	<u>L</u>	<u>G</u>	<u>T</u>	<u>E</u>	<u>T</u>	<u>I</u>	<u>D</u>
	Y	W	G	G	D	H	V	T	V	S	S										

20

FAT 94 Light Chain DNA and Amino Acid sequences

25 Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

FAT 95 Heavy Chain DNA Sequence SEQ ID NO. 209

30 CAGGTACCTTGAAGGAGTCTGGGGGAGGCTTGGTACAGCCGGCAGGCCCTGAGACTCT
 CCTGTGCGGCCTCTGGATTACCTTGTGATTATGCCATGCACTGGGTCCGGCAAGCTCC
 AGGGAAGGGCCTGGAGTGGTCTCAGGTATTAGTTGGAATAGTGGTAGCATAGGCTATGCG
 GACTCTGTGAAGGGCCGATTCAACCATCTCCAGAGACAACGCCAAGAACTCCCTGTATCTGC
 AAATGAACAGTCTGAGAGCTGAGGACACGGCCTTGTATTACTGTGGAAAAGATTGAGTGC
 GGGCGGTATGGACGTCTGGGGCAAGGGACCAACGGTCACCGTCTCCTCA

FAT 95 Heavy Chain Amino Acid sequence SEQ ID NO. 210

Q	V	T	L	K	E	S	G	G	G	L	V	Q	P	G	R	P	L	R	L	S	
C	A	A	S	G	F	T	F	D	D	Y	A	M	H	W	V	R	Q	A	P	G	
5	K	G	L	E	W	V	S	G	I	S	W	N	S	G	S	I	G	Y	A	D	S
V	K	G	R	F	T	I	S	R	D	N	A	K	N	S	L	Y	L	Q	M	N	
S	L	R	A	E	D	T	A	L	Y	Y	C	G	K	D	L	S	A	G	G	M	
D	V	W	G	Q	G	T	T	V	T	V	S	S									

10 FAT 95 Light Chain DNA Sequence SEQ ID NO. 211

CAGTCTGTGTTGACGCAGCCGCCCTCAGTGTCTGCGGCCAGGACAGTCGATCACCATCT
CCTGCACTGGAACCAGCAGTGACGTTGGTGGTTATAACTATGTCTCCTGGTACCAACAACA
CCCAGGCCAAAGCCCCAAACTCATGATTTATGAGGGCAGTAAGCGGCCCTAGGGGTCCCT
15 GACCGATTCTCTGGCTCCAAGTCTGGCAACTCAGCCTCCCTGGACATCAGTGGGCTCCAGT
CTGAGGATGAGGCTGATTATTACTGTGCAGCATGGGATGACAGCCTGAGTGAATTCTCCT
CGGAACTGGGACCAAGCTGACCGTCCTA

20 FAT 95 Light Chain Amino Acid sequence SEQ ID NO. 212

Q	S	V	L	T	Q	P	P	S	V	S	A	A	P	G	Q	S	I	T	I	S
C	T	G	T	S	S	D	V	G	G	Y	N	Y	V	S	W	Y	Q	Q	H	P
G	K	A	P	K	L	M	I	Y	E	G	S	K	R	P	L	G	V	P	D	R
F	S	G	S	K	S	G	N	S	A	S	L	D	I	S	G	L	Q	S	E	D
25 E	A	D	Y	Y	C	A	A	W	D	D	S	L	S	E	F	L	L	G	T	G
T	K	L	T	V	L															

30 FAT 96 Heavy Chain DNA Sequence SEQ ID NO. 213

GAGGTGCAGCTGGTGGAGTCTGGGCTGAGGTGAAGAAGCCTGGGCTCAGTGAAGGTCT
CCTGCAAGGCTTCCGGTTACATGTTACCAGTCACGGTATCACCTGGGTGCGACAGGCC
TGGACAAGGGCTGAGTGGATGGATGGATCAGCGGTGACAATGTTAGCACAAACTATGCA
GAGAAGCTTCTGGCAGAGTCACCATGACCACAGACACATCCACGAGTACAGCCTACATGG
AGCTGAGCAGCCTGAGATCTGAGGACACGCCGTATTACTGTGCAGTACAGGGTCCCT
35 ATTTGACTACTGGGCCGAGGCACCCGGTCACCGTCTCCTCA

FAT 96 Heavy Chain Amino Acid sequence SEQ ID NO. 214

	E	V	Q	L	V	E	S	G	A	E	V	K	K	P	G	A	S	V	K	V	S
5	C	K	A	S	G	Y	M	F	T	S	H	G	I	T	W	V	R	Q	A	P	G
	Q	G	L	E	W	M	G	W	I	S	G	D	N	V	S	T	N	Y	A	E	K
	L	L	G	R	V	T	M	T	T	D	T	S	T	S	T	A	Y	M	E	L	S
	S	L	R	S	E	D	T	A	V	Y	Y	C	A	S	T	G	S	L	F	D	Y
	W	G	R	G	T	P	V	T	V	S	S										

10

FAT 96 Light Chain DNA and Amino Acid sequences

Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

15 FAT 97 Heavy Chain DNA Sequence SEQ ID NO. 215

GAAGTGCAGCTGGTGCAGTCTGGGGCTGAGATGAAGAAGCCTGGTCCTCGGTGAAAGTCT
 CCTGCAAGGCTTCTGGAGGCACCTTCAGCACCTATATTATCAACTGGGTGCGACAGGCC
 TGGACAAGGGCTGAGTGGATGGGAGGGATCATCCCTATGTTGATAACAACAAACTACGCA
 20 CAGAAGTTCCAGGGCAGAGTCTCCATTACCGCGAACGAATCCACGAGGACAGCCTACATGG
 AGCTGAGCAGCCTGAGATCTGACGACACGCCCTCTATTACTGTGCGAGAGATCCGTTGGG
 GACCACAGGGAGCTTGATATCTGGGCAGAGGCACCCTGGTCACAGTCTCGAGT

25 FAT 97 Heavy Chain Amino Acid sequence SEQ ID NO. 216

	E	V	Q	L	V	Q	S	G	A	E	M	K	K	P	G	S	S	V	K	V	S	
	C	K	A	S	G	G	T	F	S	T	Y	I	I	I	N	W	V	R	Q	A	P	G
	Q	G	L	E	W	M	G	G	I	I	P	M	F	D	T	T	N	Y	A	Q	K	
	F	Q	G	R	V	S	I	T	A	D	E	S	T	R	T	A	Y	M	E	L	S	
30	S	L	R	S	D	D	T	A	L	Y	Y	C	A	R	D	P	L	G	T	T	G	
	<u>A</u>	<u>F</u>	<u>D</u>	<u>I</u>	W	G	R	G	T	L	V	T	V	S	S							

35

FAT 97 Light Chain DNA Sequence SEQ ID NO. 217

5 CAGTCTGTGCTGACTCAGCCTGCCTCCGTCTGGTCCCCTGGACAGTCGATCACCATCT
 CCTGCAC TGGAACCAGCAGTGACGTTGGTGGTTATAACTATGTCTCCTGGTACCAACAACA
 CCCAGGCAAAGCCCCAAACTCATGATTTATGAGGGCAGTAAGC GCCCTCAGGGTTTCT
 AATCGCTTCTCTGGCTCCAAGTCTGGCAATACGCCCTCCCTGACAATCTCTGGGCTCCAGG
 CTGAGGATGAGGCTGATTATTACTGCAGTCATATGCAGGCATCAACAATT CGGGGTGCT
 ATT CGGC GGAGGGACCAAGCTGACCGTCCTA

10 FAT 97 Light Chain Amino Acid sequence SEQ ID NO. 218

Q	S	V	L	T	Q	P	A	S	V	S	G	S	P	G	Q	S	I	T	I	S	
C	T	G	T	S	S	D	V	G	G	Y	N	Y	V	S	W	Y	Q	Q	H	P	
G	K	A	P	K	L	M	I	Y	E	G	S	K	R	P	S	G	V	S	N	R	
15	F	S	G	S	K	S	G	N	T	A	S	L	T	I	S	G	L	Q	A	E	D
E	A	D	Y	Y	C	S	S	Y	A	G	I	N	N	F	G	V	L	F	G	G	
G	T	K	L	T	V	L															

FAT 98 Heavy Chain DNA Sequence SEQ ID NO. 219

20 GAAGTGCAACTGGTGCAGTCTGGCGGAGGGTTGGTTGGCCTGGGGGTCCCTGAGACTCT
 CCTGTGAGGCTTCTGGATTCTTAGTTCAGCTAGTGGACAGATGAACTGGGTCCGCCAGGC
 TCCAGGGAAAGGGGCTGGAGTGGTCTCATTATTAGTAGTGGTAGTACCACTAC
 GCAGACTCTGTGAGGGGCCGATTACCACATCTCCAGAGACAACGCCAAGAACACACTGTATC
 25 CGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTCTATTACTGTGCGAGAGAGGCCGA
 CTACTACTACGGTATGGACGTCTGGGGCGAGGCACCC TTGTCACAGTGTGAGT

FAT 98 Heavy Chain Amino Acid sequence SEQ ID NO. 220

E	V	Q	L	V	Q	S	G	G	G	L	V	W	P	G	G	S	L	R	L	S
C	E	A	S	G	F	L	V	S	A	S	G	Q	M	N	W	V	R	Q	A	P
G	K	G	L	E	W	V	S	F	I	S	S	G	S	S	T	T	Y	Y	A	D
S	V	R	G	R	F	T	I	S	R	D	N	A	K	N	T	L	Y	P	Q	M

68

N	S	L	R	A	E	D	T	A	V	Y	Y	C	A	R	<u>E</u>	<u>A</u>	<u>D</u>	<u>Y</u>	<u>Y</u>	<u>Y</u>	
<u>G</u>	<u>M</u>	<u>D</u>	<u>V</u>	<u>W</u>	<u>G</u>	<u>R</u>	<u>G</u>	<u>T</u>	<u>L</u>	<u>V</u>	<u>T</u>	<u>V</u>	<u>S</u>	<u>S</u>							

FAT 98 Light Chain DNA and Amino Acid sequences

5

Identical to FAT 31 (SEQ ID NO.'s 87 and 88)

FAT 99 Heavy Chain DNA Sequence SEQ ID NO. 221

10 CAGGTGCAGCTGGTGCAGTCTGGGGGAGGCTTGGTACAGCCTAGGGGGCCCTGAGACTCT
 CCTGTGCAGCCTCTGGATTACCTTACAGCTATGCCATGAGCTGGGTCCGCCAGGCTCC
 AGGGAAGGGCTGGAGTGGGTCTCAGGTATTAGTGGTAGTGGTGGTCCACATACTACGCA
 GACTCAGTGAAGGGCCGATTACCACATCTCCAGAGACAACGCCAAGAACTCACTGTATCTGC
 AAATGAACAGCCTGAGAGGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGATGGAGAAGG
 15 GACTACTGGGGCCGAGGGACAATGGTCCACAGTCTCGAGT

FAT 99 Heavy Chain Amino Acid sequence SEQ ID NO. 222

Q	V	Q	L	V	Q	S	G	G	G	L	V	Q	P	R	G	P	L	R	L	S	
20	C	A	A	S	G	F	T	F	S	S	Y	A	M	S	W	V	R	Q	A	P	G
	K	G	L	E	W	V	S	G	I	S	G	S	G	G	S	T	Y	Y	A	D	S
	V	K	G	R	F	T	I	S	R	D	N	A	K	N	S	L	Y	L	Q	M	N
	S	L	R	A	E	D	T	A	V	Y	Y	C	A	R	<u>D</u>	<u>G</u>	<u>E</u>	<u>G</u>	<u>T</u>	<u>T</u>	<u>G</u>
	<u>A</u>	<u>E</u>	<u>G</u>	<u>Q</u>	<u>W</u>	<u>S</u>	<u>T</u>	<u>V</u>	<u>S</u>	<u>S</u>											

25

FAT 99 Light Chain DNA Sequence SEQ ID NO. 223

CAGTCTGTGTTGACGCAGCCGCCCTCAGTGACTGCAGGACAGAAGGTACCCATT
 CCTGCTCTGGAAAGCACCTCCAACATTGGGATAATTATGTCTCCTGGTACCAACAGCACCC
 30 AGGCAAAGCCCTCAAACCTCATGATTATGATGTCAGTAAGCGGCCCTCAGGGGTCCCTGAC
 CGATTCTCTGGCTCCAAGTCTGGCAACTCAGCCTCCCTGGACATCAGTGGCTCCAGTCTG
 AGGATGAGGCTGATTATTACTGTGCAAGCATGGGATGACAGCCTGAGTGAATTCTCTCGG
 AACTGGGACCAAGCTGACCGTCCTA

35 FAT 99 Light Chain Amino Acid sequence SEQ ID NO. 224

69

Q	S	V	L	T	Q	P	P	S	V	T	A	A	P	G	Q	K	V	T	I	S
C	S	G	S	T	S	N	I	G	N	N	Y	V	S	W	Y	Q	Q	H	P	G
K	A	L	K	L	M	I	Y	D	V	S	K	R	P	S	G	V	P	D	R	F
S	G	S	K	S	G	N	S	A	S	L	D	I	S	G	L	Q	S	E	D	E
5	A	D	Y	Y	C	A	A	W	D	D	S	L	S	E	F	L	F	G	T	G
	K	L	T	V	L															

FAT 101 Heavy Chain DNA Sequence SEQ ID NO. 225

10 GAGGTGCAGCTGGTGGAGTCCGGAGGGGGCTTGGTACAGCCTGGGGGTCCCTGAGACTCT
 CCTGTGCAGCCTCTGGATTCACCTTAGCAGCTATGCCATGAGCTGGTCCGCCAGGCTCC
 AGGGAAGGGGCAGGAGTGGGTCTCAGCTATTAGTGGTAGTGGTAGCGCATACTACGCA
 GACTCCGTGAAGGGCCGGTTCACCATCCCAGAGACAATTCCAAGAACACGCTGTATCTGC
 AAATGAACAGCCTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAGCCTATGGCAG
 15 TGAAGACTACTGGGCCAAGGAACCTGGTCACCGTCTCGAGT

FAT 101 Heavy Chain Amino Acid sequence SEQ ID NO. 226

E	V	Q	L	V	E	S	G	G	G	L	V	Q	P	G	G	S	L	R	L	S	
20	C	A	A	S	G	F	T	F	S	S	Y	A	M	S	W	V	R	Q	A	P	G
	K	G	Q	E	W	V	S	A	I	S	G	S	G	G	S	A	Y	Y	A	D	S
	V	K	G	R	F	T	I	P	R	D	N	S	K	N	T	L	Y	L	Q	M	N
	S	L	R	A	E	D	T	A	V	Y	Y	C	A	K	A	Y	G	S	E	D	Y
	W	G	Q	G	T	L	V	T	V	S	S										

25

FAT 101 Light Chain DNA and Amino Acid sequences

Identical to FAT 44 (SEQ ID NO.'s 115 and 116)

30 FAT 102 Heavy Chain DNA Sequence SEQ ID NO. 227

10 CAGGTACCTTGAAGGAGTCTGGGGAGGCGTGGTCCAACCTGGAGGTCCCTGAGACTCT
 CCTGTGCAGCCTCTGAATTAGCCTCAGTAGCCATGCTATGCACTGGTCCGCCAGGCTCC
 AGGCAAGGGCTGGAGTGGGTGGCCAACATAAAGGGAGATGGAAGTGCAGACTCTGTG
 35 GACTCTATGAAGGGCCGATTCAACCATCCCCAGAGACAACGCCAAAGACTCAGTGTATCTGG

70

AAATGACCAGCCTGAGAGCCGAGGACACGGCCGTGTACTACTGTGCGAGAGACCTGAACCC
 GGGCCAGGGGGGGACATATTATGATGCTTTGACATTGGGGCAAGGCACCCCGGTACCC
 GTCTCCTCA

5

FAT 102 Heavy Chain Amino Acid sequence SEQ ID NO. 228

10	Q	V	T	L	K	E	S	G	G	G	V	V	Q	P	G	R	S	L	R	L	S
	C	A	A	S	E	F	S	L	S	S	H	A	M	H	W	V	R	Q	A	P	G
	K	G	L	E	W	V	A	N	I	K	G	D	G	S	A	K	Y	S	V	D	S
	M	K	G	R	F	T	I	P	R	D	N	A	K	D	S	V	Y	L	E	M	T
	S	L	R	A	E	D	T	A	V	Y	Y	C	A	R	<u>D</u>	<u>L</u>	<u>N</u>	<u>P</u>	<u>G</u>	<u>Q</u>	<u>G</u>
15	<u>G</u>	<u>T</u>	<u>Y</u>	<u>Y</u>	<u>D</u>	<u>A</u>	<u>F</u>	<u>D</u>	<u>I</u>												

FAT 102 Light Chain DNA and Amino Acid sequences

Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

20

FAT 103 Heavy Chain DNA Sequence SEQ ID NO. 229

GAGGTCCAGCTGGTGCAGTCTGGGGAGGCTGGTCCAGCCTGGGGGTCCCTGAAACTCT
 CCTGTGCAGCCTCTGGGTTCACCTCAGTGGCTCTGCTATGCACTGGTCCGCCAGGCTTC
 25 CGGGAAAGGGCTGGAGTGGGTTGCCGTATTAGAACGAAAGCTAACAGTTACCGACAGCA
 TATGCTCGTCGGTGAAAGGCAGGTTACCACCTCCAGAGATGATTCAAAGAACACGGCGT
 ATCTGCAAATGAACAGCCTGAAACCCGAGGACACGGCGTGTATTACTATACTAGACCTGG
 AGATAGCAGTGGCGGTATGGGGAGGGACTACTGGGGCAGGGCACCCTGGTACCGTCTCG
 AGT

30

FAT 103 Heavy Chain Amino Acid sequence SEQ ID NO. 230

35	E	V	Q	L	V	Q	S	G	G	G	L	V	Q	P	G	G	S	L	K	L	S
	C	A	A	S	G	F	T	F	S	G	S	A	M	H	W	V	R	Q	A	S	G
	K	G	L	E	W	V	G	R	I	R	S	K	A	N	S	Y	A	T	A	Y	A

71

A	S	V	K	G	R	F	T	I	S	R	D	D	S	K	N	T	A	Y	L	Q	
M	N	S	L	K	T	E	D	T	A	V	Y	Y	Y	T	R	<u>P</u>	<u>G</u>	<u>D</u>	<u>S</u>	<u>S</u>	
<u>G</u>	<u>G</u>	<u>M</u>	<u>G</u>	<u>R</u>	<u>D</u>	<u>Y</u>	<u>W</u>	<u>G</u>	<u>R</u>	<u>G</u>	<u>T</u>	<u>L</u>	<u>V</u>	<u>T</u>	<u>V</u>	<u>S</u>	<u>S</u>				

5 FAT 103 Light Chain DNA and Amino Acid sequences

Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

FAT 104 Heavy Chain DNA Sequence SEQ ID NO. 231

10 GAGGTGCAGCTGGTGGAGTCTGGGGGAGGTTGGTACAGCCTGGCAGGTCCCTGAGACTCT
 CCTGTGCAGCCTCTGGATTCACCTTGATGATTATGCCATGCACTGGGTCCGGCAAGCTCC
 AGGGAAGGGGCTGGAGTGGGTTTCATACATTAGTAGTAGTAGTTACACAAACTACGCA
 GACTCTGTGAAGGGCCGATTCAACCCTCCAGAGACAACGCCAAGAACTCACTGTATCTGC
 15 AAATGAACAGCCTGAGAGCCGAGGACACGCCGTGTATTACTGTGCGAGAGGATCGCGTA
 TTACGATATTTGACTGGCTCGGGGATGATGCTTTGATATCTGGGCCGAGACACCTG
 GTCACCGTCTCGAGT

FAT 104 Heavy Chain Amino Acid sequence SEQ ID NO. 232

20 E V Q L V E S G G G L V Q P G R S L R L S
 C A A S G F T F D D Y A M H W V R Q A P G
 K G L E W V S Y I S S S S S Y T N Y A D S
 V K G R F T I S R D N A K N S L Y L Q M N
 25 S L R A E D T A V Y Y C A R G S A Y Y D I
 L T G S G D D A F D I W G R D T L V T V S
 S

FAT 104 Light Chain DNA and Amino Acid sequences

30 Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

FAT 105 Heavy Chain DNA sequence SEQ ID NO. 233

GGGGTGCAGCTGGTCCATTCTGGGGCTGAGGTGAAGAAGCCTGGTCTCGGTGAAGTTCT
 CCTGCAAGGCTTCTGGAGACACTTCAACACTTATGTTATCAACTGGGTGCGACAGGCC
 TGGACAAGGGCTTGAGTGGATGGGAGGGATCATCCCTATGTTGGAACAGCAAGCCACGCA
 CAGAAGTTTCAGGGCAGAGTCACACTTACCGCGGACGAATCTATTAAACACAGTGTACATGG
 5 AGCTGAGCAGGGCTCAGGTATGACGACGCGGCCGTATATTATTGTGCGCGAGAAGTTATATT
 CTTCTCCGAAGGCATGGACGTCTGGGGCAGAGGAACCCTGGTCACCGTCTCGAGT

FAT 105 Heavy Chain Amino Acid sequence SEQ ID NO. 234

10	G	V	Q	L	V	H	S	G	A	E	V	K	K	P	G	S	S	V	K	F	S	
	C	K	A	S	G	D	T	F	N	T	Y	V	I	N	W	V	R	Q	A	P	G	
	Q	G	L	E	W	M	G	G	I	I	P	M	F	G	T	A	S	H	A	Q	K	
	F	Q	G	R	V	T	L	T	A	D	E	S	I	N	T	V	Y	M	E	L	S	
	G	L	R	Y	D	D	A	A	V	Y	Y	C	A	R	<u>E</u>	V	I	F	F	S	E	
15	<u>G</u>	<u>M</u>	<u>D</u>	<u>V</u>	W	G	R	G	T	L	V	T	V	S	S							

FAT 105 Light Chain DNA sequence SEQ ID NO. 235

CAGTCTGTGCTGACTCAGCCACCCCTCAGCGTCTGGGACCCCCGGCAGAGGGCACCATCT
 20 CTTGTTCTGGAAGCAGCTCCAACATCGGGAGTAACACTGTAAACTGGTACCAGCGACTCCC
 AGGAGCAGGGCCCCCAACTCCTCATCTACAATAATGACCAGCAGCCCTCAGGGATCCCTGAC
 CGATTCTCTGGCTCCAAGTCTGGCACCTCAGGCTCCCTGGTCATCAGTGGCTCCAGTCTG
 AAGATGAGGCTGATTACTACTGTGCGTCATGGGATGACAGTCTGAATGGTCGGGTGTTCGG
 CGGAGGGACCAAGCTGACCGTCCTA
 25

FAT 105 Light Chain Amino Acid sequence SEQ ID NO. 236

	Q	S	V	L	T	Q	P	P	S	A	S	G	T	P	G	Q	R	A	T	I	S
	C	S	G	S	S	S	N	I	G	S	N	T	V	N	W	Y	Q	R	L	P	G
30	A	A	P	Q	L	L	I	Y	N	N	D	Q	R	P	S	G	I	P	D	R	F
	S	G	S	K	S	G	T	S	G	S	L	V	I	S	G	L	Q	S	E	D	E
	A	D	Y	Y	C	A	S	W	D	D	S	L	N	G	R	V	F	G	G	G	T
	K	L	T	V	L																

35 FAT 106 Heavy Chain DNA sequence SEQ ID NO. 237

CAGGTGCAGCTGCAGGAGTCGGGGCTGAGGTGAAGAAGCCTGGTCCTCGCTGAAGGTTT
 CGGCCAGGCTTCTGCAGGCACCTCAACAGCCATGCTATCGGCTGGTGCAGGCC
 TGGACAAGGGCTTGAGTGGATGGATGGATCAATCCTAACAGTGGTGGCACAAACTATGCA
 GAGAAATTCAGGGCAGGGTCACCCCTGACCAGGGACGCCATCAGTACAGCGTACTTGG
 5 AGCTGAGCAGGCTGACATCTGACGACACGCCATGTATTACTGTGCGAGAGATATCGATGA
 TAGTGGTTATCAATACTGGGCCAGAGCACCCCTGGTACCGTCTTTCC

FAT 106 Heavy Chain Amino Acid sequence SEQ ID NO. 238

10	Q	V	Q	L	Q	E	S	G	A	E	V	K	K	P	G	S	S	L	K	V	S
	C	Q	A	S	A	G	T	F	N	S	H	A	I	G	W	V	R	Q	A	P	G
	Q	G	L	E	W	M	G	W	I	N	P	N	S	G	G	T	N	Y	A	E	K
	F	Q	G	R	V	T	L	T	R	D	A	A	I	S	T	A	Y	L	E	L	S
	R	L	T	S	D	D	T	A	M	Y	Y	C	A	R	<u>D</u>	<u>I</u>	<u>D</u>	<u>D</u>	<u>S</u>	<u>G</u>	<u>Y</u>
15	<u>Q</u>	<u>Y</u>	W	G	Q	S	T	L	V	T	V	S	S								

FAT 106 Light Chain DNA sequence SEQ ID NO. 239

CAGTCTGTGCTGACTCAGCCTGCCTCCGTCTGGTCTCCTGGACAGTCGATCACCAC
 20 CCTGCACTGGAACCAGCAGTGACGTTGGTGGTTATAACTATGTCTCCTGGTACCAACAGCA
 CCCAGGCAAAGCCCCAAACTCATGATTATGAGGTCAATAAGGCCCTCAGGGTCCCT
 GATCGCTTCTCTGGCTCCAAGTCTGGAACACGCCCTCCCTGACCGTCTCTAGACTCCAGG
 CTGAGGATGAGGCTGATTATTACTGCAGCTCATATGCAGGAAACGACAGTGTGCTTTCGG
 CGGAGGGACCAAGCTGACCGTCCTA
 25

FAT 106 Light Chain Amino Acid sequence SEQ ID NO. 240

	Q	S	V	L	T	Q	P	A	S	V	S	G	S	P	G	Q	S	I	T	I	S
	C	T	G	T	S	S	D	V	G	G	Y	N	Y	V	S	W	Y	Q	Q	H	P
30	G	K	A	P	K	L	M	I	Y	E	V	N	K	R	P	S	G	V	P	D	R
	F	S	G	S	K	S	G	N	T	A	S	L	T	V	S	R	L	Q	A	E	D
	E	A	D	Y	Y	C	S	S	Y	A	G	N	D	S	V	L	F	G	G	G	T
	K	L	T	V	L																

35 FAT 107 Heavy Chain DNA Sequence SEQ ID NO. 241

CAGGTACAGCTGCAGCAGTCAGGCCAGGGCTGGTGAAGCCTCGGGGACCTGTCCCTCA
 CCTGCGGTGTCTCTGGTGAECTCCATGAGTGGTAATAACCGGTGGAGTTGGGTCCGCCAGTC
 CCCAGGGAAAGGGCTGGAGTGGGTCTCAGCTATTAGTGGTAGTGGTAGCACATACTAC
 GCAGACTCCGTGAAGGGCCGATTACCATCTCCAGAGACAATTCCAAGAACACGCTGTATT
 5 TGCAAATGAACAGCCTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGGCAGACACATA
 TAGTGGCTACGATGAGGCCCAACAAACTGGGGCCGAGGCACCCTGGTCACGGTATCGAGT

FAT 107 Heavy Chain Amino Acid sequence SEQ ID NO. 242

10	Q	V	Q	L	Q	Q	S	G	P	G	L	V	K	P	S	G	T	L	S	L	T
	C	G	V	S	G	D	S	M	S	G	N	N	R	W	S	W	V	R	Q	S	P
	G	K	G	L	E	W	V	S	A	I	S	G	S	G	G	S	T	Y	Y	A	D
	S	V	K	G	R	F	T	I	S	R	D	N	S	K	N	T	L	Y	L	Q	M
	N	S	L	R	A	E	D	T	A	V	Y	Y	C	A	A	<u>D</u>	T	Y	S	G	Y
15	<u>D</u>	<u>E</u>	<u>A</u>	<u>P</u>	<u>T</u>	<u>N</u>	W	G	R	G	T	L	V	T	V	S	S				

FAT 107 Light Chain DNA and Amino Acid sequences

Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

20

FAT 108 Heavy Chain DNA Sequence SEQ ID NO. 243

CAGGTGCAGCTGGTGCAGTTGGGCTGAGGTGAAGAAGCCTGGGCCTCAGTGAAGGTCT
 CCTGCAAGACTTCTGGATACAGCTTCACAAATTATGATATCAACTGGGTGCGACAGGCCGC
 25 TGGGCAAGGGCTTGAGTGGATGGATGGATCAGCGCTCACAAATGGTACACAAACTACGCA
 CAGAAGGTCCAGGGCAGAGTCACCATGACCACAGACACATCCACGACCATAGGCTACATGG
 AGCTGAGGAGCCTGAGATCTGACGACACGGCGTGTATTACTGTGCGAGAGCCTAACCT
 GGGCGACAGTGACTACGAGTTGGAGGGTATGCTTTGATATCTGGGCCAAGGGACAATG
 GTCACCGTATCGTCA

30

FAT 108 Heavy Chain Amino Acid sequence SEQ ID NO. 244

35

75

Q	V	Q	L	V	Q	F	G	A	E	V	K	K	P	G	A	S	V	K	V	S	
C	K	T	S	G	Y	S	F	T	N	Y	D	I	N	W	V	R	Q	A	A	G	
Q	G	L	E	W	M	G	W	I	S	A	H	N	G	D	T	N	Y	A	Q	K	
V	Q	G	R	V	T	M	T	T	D	T	S	T	T	I	G	Y	M	E	L	R	
5	S	L	R	S	D	D	T	A	V	Y	Y	C	A	R	<u>A</u>	F	N	L	G	D	S
	D	Y	E	L	E	G	D	A	F	D	I	W	G	Q	G	T	M	V	T	V	S
		S																			

FAT 108 Light Chain DNA and Amino Acid sequences

10

Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

FAT 109 Heavy Chain DNA Sequence SEQ ID NO. 245

15	CAGGTGCAGCTGGTGCAGTTGGGGAGGCTGGTCAGCCTGGCAGGTCCCTGAGACTCT
	CCTGTGCAGCCTCTGGATTCACCTTGATGATTATGCCATGCACTGGTCCGGCAAGCTCC
	AGGGAAGGGCCTGGAGTGGGTCTCAGGTATTAGTTGGAATAGTGGTAGCATAGGCAATGCG
	GACTCTGTGAAGGGCCGATTACCATTCCAGAGACAACGCCAAGAACTCCCTGTATCTGC
	AAATGAACAGTTGAGAGCTGAGGACACGGCCTTGTATTACTGTGCAAAAGATATTCAA
20	CATTGTATTAGCACCAGCTGCCACTACATCCACTTTGACTACTGGGGAGGGGACCACG
	GTCACCGTATCGAC

FAT 109 Heavy Chain Amino Acid sequence SEQ ID NO. 246

25	Q	V	Q	L	V	Q	F	G	G	G	L	V	Q	P	G	R	S	L	R	L	S
	C	A	A	S	G	F	T	F	D	D	Y	A	M	H	W	V	R	Q	A	P	G
	K	G	L	E	W	V	S	G	I	S	W	N	S	G	S	I	G	N	A	D	S
	V	K	G	R	F	T	I	S	R	D	N	A	K	N	S	L	Y	L	Q	M	N
	S	L	R	A	E	D	T	A	L	Y	Y	C	A	K	<u>D</u>	I	S	N	I	V	L
30	<u>A</u>	P	A	A	T	T	S	H	F	D	Y	W	G	R	G	T	T	V	T	V	S

FAT 109 Light Chain DNA and Amino Acid sequences

Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

35

FAT 110 Heavy Chain DNA Sequence SEQ ID NO. 247

GAGGTGCAGCTGGTGGAGTCTGGAGCTGAGGTGAAGCAGCCTGGGCCTCAGTGAAGGTCT
 CCTGCCAGGCCTCTGGTTACTCCTTAGCAGTCATGGTATCAGCTGGGTGCGACAGGCC
 5 AGGACAAGGGCTTGAGTGGATGGATGGATCAGCGCTTACAAGGGAAACACAAACTATACA
 CAGAAGCTCCAGGGCAGAGTCACCATGACCACAGACCCATCGACGAGCACAGCCTACATGG
 AACTGAGGAGCCTGAGACCTGACGACACGCCATGTATTACTGTGCGAGCCAATATGACAT
 TATGACTGCTTATCACACTCATGGAATGGACGTCTGGGGCGGGGACACGGTCACCGTC
 TCGAGT

10

FAT 110 Heavy Chain Amino Acid sequence SEQ ID NO. 248

E	V	Q	L	V	E	S	G	A	E	V	K	Q	P	G	A	S	V	K	V	S	
C	Q	A	S	G	Y	S	F	S	S	H	G	I	S	W	V	R	Q	A	P	G	
15	Q	G	L	E	W	M	G	W	I	S	A	Y	K	G	N	T	N	Y	T	Q	K
L	Q	G	R	V	T	M	T	T	D	P	S	T	S	T	A	Y	M	E	L	R	
S	L	R	P	D	D	T	A	M	Y	Y	C	A	S	Q	Y	D	I	M	T	A	
<u>Y</u>	<u>H</u>	<u>T</u>	<u>H</u>	<u>G</u>	<u>M</u>	<u>D</u>	<u>V</u>	<u>W</u>	<u>G</u>	<u>R</u>	<u>G</u>	<u>T</u>	<u>T</u>	<u>V</u>	<u>T</u>	<u>V</u>	<u>S</u>	<u>S</u>			

20 FAT 110 Light Chain DNA and Amino Acid sequences

Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

FAT 111 Heavy Chain DNA Sequence SEQ ID NO. 249

25

GAGGTGCAGCTGATGGAGTCGGGGCTGAGGTGAAGAAGCCTGGTCCTCGGTGAAGGTCT
 CCTGCAAGGCTTCTGGAGGCACCTTCAGCAACTCTCCTATCAACTGGCTGCGACAGGCC
 TGGACAAGGGCTTGAGTGGATGGGAAGTATCATTCCCTCCTTGGTACAGCAAACATACGCT
 CAGAAGTTCCAGGGCAGACTCACGATTACCGCGGACGAATCCACGAGCACAGCCTACATGG
 30 AGCTGAGCAGCCTGAGATCCGAGGACACGGCCGTATTACTGTGCGGCAGATAGTGGCTA
 CGATTCTCCGTTCTACTGGGGAAAGGGGACACGGTCACCGTCTCGAGT

FAT 111 Heavy Chain Amino Acid sequence SEQ ID NO. 250

E	V	Q	L	M	E	S	G	A	E	V	K	K	P	G	S	S	V	K	V	S	
C	K	A	S	G	G	T	F	S	N	S	P	I	N	W	L	R	Q	A	P	G	
Q	G	L	E	W	M	G	S	I	I	P	S	F	G	T	A	N	Y	A	Q	K	
F	Q	G	R	L	T	I	T	A	D	E	S	T	S	T	A	Y	M	E	L	S	
5	S	L	R	S	E	D	T	A	V	Y	Y	C	A	A	<u>D</u>	S	G	Y	D	S	P
	<u>F</u>	<u>Y</u>	W	G	K	G	T	T	V	T	V	S	S								

FAT 111 Light Chain DNA and Amino Acid sequences

10 Identical to FAT 31 (SEQ ID NO.'s 87 and 88)

FAT 112 Heavy Chain DNA Sequence SEQ ID NO. 251

15 GAGGTACACCTTGAAGGAGTCTGGGGAGGCTTAGTCAAGCCTGGAGGGTCCCTGAGACTCT
CCTGTGCAGCCTCTAATTTCACCTTCAGTGACTTCTACATGAGCTGGATCCGCCAGGCTCC
AGGGAAGGGGCTGGAGTGGTTTCATACATTAGTAGTATCAGAGGTACTTACACAAAGTAC
20 GCAGACTCTGTGAAGGGCCGATTCAACCATCTCCAGAGACAACGCCAAGAACTCACTGTATC
TGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTATATCACTGTGCGAGAGATTTGA
CTCCGGTGGTAACCTCCGCCATTTGATATCTGGCAAAGGACCACGTCACCGTCTCCTCC

FAT 112 Heavy Chain Amino Acid sequence SEQ ID NO. 252

25 E V T L K E S G G G L V K P G G S L R L S
C A A S N F T F S D F Y M S W I R Q A P G
K G L E W V S Y I S S I R G T Y T K Y A D
S V K G R F T I S R D N A K N S L Y L Q M
30 N S L R A E D T A V Y H C A R D F D S G G
N S A I F D I W A K D H V T V S S

FAT 112 Light Chain DNA Sequence SEQ ID NO. 253

35 CAGTCTGTGTTGACGCAGCCTCCCTCAGTGTATGCGGCCCCAGGACAGAAGGTACCCATT
CCTGCTCTGGAAGGCACCTCCAACATTGGGAATAATTATGTCTCCTGGTACCAACAGCACCC

AGGCAAAGCCCCAAACTCATGATTTATGATGTCAGTAAGCGGCCCTCAGGGGTTCTAAT
 CGCTTCTCTGGCTCCAAGTCTGGCAACTCAGCCTCCCTGGACATCAGTGGCTCCAGTCTG
 AGGATGAGGCTGATTATTACTGTGCAGCATGGGATGACAGCCTGAGTGAATTCTCTTCGG
 AACTGGGACCAAGCTGACCGTCCTA

5

FAT 112 Light Chain Amino Acid sequence SEQ ID NO. 254

10	Q	S	V	L	T	Q	P	P	S	V	Y	A	A	P	G	Q	K	V	T	I	S
	C	S	G	S	T	S	N	I	G	N	N	Y	V	S	W	Y	Q	Q	H	P	G
	K	A	P	K	L	M	I	Y	D	V	S	K	R	P	S	G	V	S	N	R	F
	S	G	S	K	S	G	N	S	A	S	L	D	I	S	G	L	Q	S	E	D	E
	A	D	Y	Y	C	A	A	W	D	D	S	L	S	E	F	L	F	G	T	G	T
15	K	L	T	V	L																

FAT 113 Heavy Chain DNA Sequence SEQ ID NO. 255

20	CAGGTGCAGCTGGTGGAGTCTGGGGCTGAGGTGAAGAAGCCTGGTCCTCGCGAAGGTCT
	CTTGCAAGGCTTGTGGAGGCACCTTCAGCAGATATGCTATCAACTGGGTGCGACAGGCC
	TGGGCAAGGGCTTGAGTGGATGGGAGCAATCCTCCCTGTCTTGGTACAACAAACTACGCT
	CAGAAGCTCCAGGGCAGAGTCACCATGACCGAGGACACATCTACAGACACAGCCTATATGG
	AGCTGAGAAGGCTGACATCTGAGGACACGGCCGTGTATTACTGTGCAACATGTGCGGAATT
	TTGTAGTGATTCCAAGTGCCCTCTAGACCCCTGGGGCAAAGGGACAGTGGTCACCGTCTCC
25	TCCA

FAT 113 Heavy Chain Amino Acid sequence SEQ ID NO. 256

30	Q	V	Q	L	V	E	S	G	A	E	V	K	K	P	G	S	S	A	K	V	S
	C	K	A	C	G	G	T	F	S	R	Y	A	I	N	W	V	R	Q	A	P	G
	Q	G	L	E	W	M	G	A	I	L	P	V	F	G	T	T	N	Y	A	Q	K
	L	Q	G	R	V	T	M	T	E	D	T	S	T	D	T	A	Y	M	E	L	R
	R	L	T	S	E	D	T	A	V	Y	Y	C	A	T	<u>C</u>	<u>A</u>	<u>E</u>	<u>F</u>	<u>C</u>	<u>S</u>	<u>D</u>
	<u>S</u>	<u>N</u>	<u>C</u>	<u>P</u>	<u>L</u>	<u>D</u>	<u>P</u>	<u>W</u>	<u>G</u>	<u>K</u>	<u>G</u>	<u>T</u>	<u>V</u>	<u>V</u>	<u>T</u>	<u>V</u>	<u>S</u>	<u>S</u>			

35

79

FAT 113 Light Chain DNA Sequence SEQ ID NO. 257

CAGTCTGTGTTGACGCAGCCGCCCTCAGTGTCTGCGGCCCCAGGACAGAAGGTACCCATT
 CCTGCTCTGGAAGCACCTCCAACATTGGGATAATTATGTCTCCTGGTACCAACAGCACCC
 5 AGGCAAAGCCCCAAACTCATGATTTATGATGTCAGTAAGCGGCCCTCAGAGGTCCCTGAC
 CGATTCTCTGGCTCCAAGTATGGCAACTCAGCCTCCCTGGACATCAGTGGCTCCAGTCAG
 AGGATGAGGCTGATTATTACTGTGCAGCATGGATGACAGCCTGAGTGAATTCTCTCGG
 AACTGGGACCAAGCTGACCGTCCTA

10 FAT 113 Light Chain Amino Acid sequence SEQ ID NO. 258

Q	S	V	L	T	Q	P	P	S	V	S	A	A	P	G	Q	K	V	T	I	S	
C	S	G	S	T	S	N	I	G	N	N	Y	V	S	W	Y	Q	Q	H	P	G	
K	A	P	K	L	M	I	Y	D	V	S	K	R	P	S	E	V	P	D	R	F	
15	S	G	S	K	Y	G	N	S	A	S	L	D	I	S	G	L	Q	S	E	D	E
A	D	Y	Y	C	A	A	W	D	D	S	L	S	E	F	L	F	G	T	G	T	
K	L	T	V	L																	

FAT 114 Heavy Chain DNA Sequence SEQ ID NO. 259

20 CAGGTGCAGCTGCAGGAGTCGGGCCAGGACTGGTGAAGCTTCGGGAATCTGTCCCTCA
 CCTGCGCTGTCTGGTGTGTCCTCAGCAGTAGTGACTGGTGGTGGCTCCACCAGGCTCC
 AGGCAAGGGGCTGGAGTGGGTGGCAGTTATCATATGATGGAAGTAATAAACTACGCA
 GACTCCGTGAAGGGCCGATTCAACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGC
 25 AAATGAACAGCCTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAGATATAGCAGA
 GGGCGTAGGCTACTACATGAACGTCTGGGCCAAGGGACAATGGTCACCGTCTCTCA

FAT 114 Heavy Chain Amino Acid sequence SEQ ID NO. 260

Q	V	Q	L	Q	E	S	G	P	G	L	V	K	L	S	G	N	L	S	L	T
C	A	V	S	G	V	S	L	S	S	S	D	W	W	W	L	H	Q	A	P	G
K	G	L	E	W	V	A	V	I	S	Y	D	G	S	N	K	Y	Y	A	D	S
V	K	G	R	F	T	I	S	R	D	N	S	K	N	T	L	Y	L	Q	M	N

80

S	L	R	A	E	D	T	A	V	Y	Y	C	A	K	<u>D</u>	I	A	E	G	V	G
<u>Y</u>	<u>Y</u>	<u>Y</u>	M	N	V	W	G	Q	G	T	M	V	T	V	S	S				

FAT 114 Light Chain DNA and Amino Acid sequences

5

Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

FAT 115 Heavy Chain DNA Sequence SEQ ID NO. 261

10 GGGGTGCAGCTGGTGGAGTCCGGGGAGCCTTGGCACAGCCTGGGGGTCCCTAAGACTTT
 CTTGTGCAGCCTCTGGATTACGTTAGCAGCTATGCCATGATCTGGTCCGCCAGGCTCC
 AGGGAAGGGGCTGGAGTGGGTCTCTTCTATCAGTGGTAGTGGTGGCACATATTACGCA
 GACTCCGTGAAGGGCCGGTTCACCGTCTCCAGAGACAATTCCAAGAACACGGTGTATCTGC
 AGATGAACAGTCTGAGAGGCCGGGACACGCCGTTATTATTGTGCGAAGAGGGCCAACTA
 15 CTACTACTGGACGTCTGGGCCGAGGAACCATTGTGCCGTGG

FAT 115 Heavy Chain Amino Acid sequence SEQ ID NO. 262

G	V	Q	L	V	E	S	G	G	A	L	A	Q	P	G	G	S	L	R	L	S	
20	C	A	A	S	G	F	T	F	S	S	Y	A	M	I	W	V	R	Q	A	P	G
	K	G	L	E	W	V	S	S	I	S	G	S	G	G	G	T	Y	Y	A	D	S
	V	K	G	R	F	T	V	S	R	D	N	S	K	N	T	V	Y	L	Q	M	N
	S	L	R	A	G	D	T	A	V	Y	Y	C	A	K	<u>R</u>	<u>A</u>	<u>N</u>	<u>Y</u>	<u>Y</u>	<u>L</u>	
	<u>D</u>	<u>V</u>	<u>W</u>	<u>G</u>	<u>R</u>	<u>G</u>	<u>T</u>	<u>I</u>	<u>V</u>	<u>P</u>	<u>W</u>										

25

FAT 115 Light Chain DNA Sequence SEQ ID NO. 263

TCGTCTGAGCTGACTCAGGACCCTGCTGTGTCTGGCCTGGGACAGACAGTCAGGATCA
 CATGCCAAGGAGACAGCCTCAGAACAGCTATTATGCAAGCTGGTACCGAGCAGGCCAGGACA
 30 GGCCCCTGTACTTGTCTATGGAAAAATAAGCCGCCCTCAGGGATCCCAGACCGACTC
 TCTGGCTCCAGCTCAGGAAACACAGCTTCCATTGACCATCACTGGGCTCAGGCAGGAGGATG
 AGGCTGACTATTACTGTAACCTCCGGGACATCAGTGGTAACCATGTGCTTTGGCGGAGG
 GACCAAGCTGACCGTCCTA

35 FAT 115 Light Chain Amino Acid sequence SEQ ID NO. 264

81

S	S	E	L	T	Q	D	P	A	V	S	V	A	L	G	Q	T	V	R	I	T	
C	Q	G	D	S	L	R	S	Y	Y	A	S	W	Y	Q	Q	K	P	G	Q	A	
P	V	L	V	I	Y	G	K	N	K	R	P	S	G	I	P	D	R	L	S	G	
S	S	S	G	N	T	A	S	L	T	I	T	G	A	Q	A	E	D	E	A	D	
5	Y	Y	C	N	S	R	D	I	S	G	N	H	V	L	F	G	G	G	T	K	L
	T	V	L																		

FAT 116 Heavy Chain DNA Sequence SEQ ID NO. 265

10 GAGGTGCAGCTGGTGGAGTTGGGGAGGCTGGTCAAGCCTGGAGAGTCCTGAGACTCT
 CCTGTGCAGCCTCTGGATTACACCTTCAGTGAECTACATGAGCTGGATCCGCCAGGCTCC
 AGGGAAGGGCTGGAGTGGGTTTCATACATTAGTAGTAGTAGTTACACAAACTACGCA
 GACTCTGTGAAGGGCCGATTCAACCATCTCCAGAGACAACGCCAAGAACTCACTGTATTGC
 15 AAATGAACAGCCTGAGAGCCGAGGACACGCCGTGTATTACTGTGCGAGAGGCCGGACCCA
 GTGCTCATTGGCGTCTGTGCGACGGGAGGTTGGGCCAGGGACCCTGGTCACCGTCTCG
 AGT

FAT 116 Heavy Chain Amino Acid sequence SEQ ID NO. 266

20 E V Q L V E F G G G L V K P G E S L R L S
 C A A S G F T F S D Y Y M S W I R Q A P G
 K G L E W V S Y I S S S S S Y T N Y A D S
 V K G R F T I S R D N A K N S L Y L Q M N
 S L R A E D T A V Y Y C A R G G T Q C S F
 25 G V C A T G G W G Q G T L V T V S S

FAT 116 Light Chain DNA and Amino Acid sequences

Identical to FAT 31 (SEQ ID NO.'s 87 and 88)

30

FAT 117 Heavy Chain DNA Sequence SEQ ID NO. 267

CAGGTGCAGCTGGTGGAGTCTGGGGAGGCGTGGTCCAGCCTGGAGGGTCCCTGAGACTCT
 CCTGTGCAGCCTCTGGATTACACCTTCAGTGAACCACATGGACTGGGTCCGCCAGGCTCC
 35 AGGGAAGGGCTGGAGTGGTGGCCAACATAAACCGAGATGGAAGTGACTACCGCTATGTG

GA
CTCTGTGAAGGGCCGATT
CACCATCTCCAGAGACGACGCCAAGAA
CTGTATCTCC
AA
ATGAACAGTCTGAGAGCCGAGGACACGGCCGT
TATTACTGTGC
GAGAGGCCGGGTTCTG
CCTTAACCCTGTGT
TTATCATGGAGGTTGGGGCCAGGG
ACCCTGGTCACC
GCCCTCCTCA

5

FAT 117 Heavy Chain Amino Acid sequence SEQ ID NO. 268

10	Q	V	Q	L	V	E	S	G	G	G	V	V	Q	P	G	G	S	L	R	L	S	
	C	A	A	S	G	F	T	F	S	D	H	H	M	D	W	V	R	Q	A	P	G	
	K	G	L	E	W	V	A	N	I	N	R	D	G	S	D	Y	R	Y	V	D	S	
	V	K	G	R	F	T	I	S	R	D	D	A	K	N	S	L	Y	L	Q	M	N	
	S	L	R	A	E	D	T	A	V	Y	Y	C	A	R	<u>G</u>	<u>G</u>	<u>F</u>	<u>C</u>	<u>L</u>	<u>N</u>	<u>P</u>	
15	<u>V</u>	<u>C</u>	<u>Y</u>	<u>H</u>	<u>G</u>	<u>G</u>	<u>W</u>	<u>G</u>	<u>Q</u>	<u>G</u>	<u>T</u>	<u>L</u>	<u>V</u>	<u>T</u>	<u>A</u>	<u>S</u>	<u>S</u>					

FAT 117 Light Chain DNA and Amino Acid sequence

Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

20

FAT 118 Heavy Chain DNA Sequence SEQ ID NO. 269

GAGGTGCAGCTGGTGGAGTTGGAGCTGAGGTGAAGAAGCCTGGGGCTCAGTGAAGGTTT
CCTGCAAGGCCTCTGATTACACCTTACCA
GCTATGGTATCAGCTGGGTGCGACAGGCC
25 TGGACAAGGGCTTGAGTGGATGGAGCAGCGCTAACGATGGTAACACAA
ACTATGCA CAGAAGCTCCAGGGCAGAGTCACCATGACCACAGACACATCCAC
GAGCAGCAGCCTACATGG AGTTGAGGAGCCTGAGATCTGACGACACGGCGTGT
ATTACTGTGC
GAGAGGCCAGGGACCCTGGTCACCGTCTCC
CTGCCCTTGTGCCTGTTGCTCCGGAGGTTGGGGCC
30 TCA

30

FAT 118 Heavy Chain Amino Acid sequence SEQ ID NO. 270

35	E	V	Q	L	V	E	F	G	A	E	V	K	K	P	G	A	S	V	K	V	S
	C	K	A	S	D	Y	T	F	T	S	Y	G	I	S	W	V	R	Q	A	P	G
	Q	G	L	E	W	M	G	W	S	S	A	N	D	G	N	T	N	Y	A	Q	K

83

L	Q	G	R	V	T	M	T	T	D	T	S	T	S	T	A	Y	M	E	L	R	
S	L	R	S	D	D	T	A	V	Y	Y	C	A	R	<u>G</u>	<u>G</u>	<u>L</u>	<u>P</u>	<u>C</u>	<u>P</u>	<u>C</u>	
<u>A</u>	<u>A</u>	<u>C</u>	<u>C</u>	<u>S</u>	<u>G</u>	<u>G</u>	<u>W</u>	<u>G</u>	<u>Q</u>	<u>G</u>	<u>T</u>	<u>L</u>	<u>V</u>	<u>T</u>	<u>V</u>	<u>S</u>	<u>S</u>				

5 FAT 118 Light Chain DNA and Amino Acid sequences

Identical to FAT 30 (SEQ ID NO.'s 83 and 84)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/03900A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/13 C07K16/28 C12N5/10 C12N15/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, MEDLINE, STRAND, BIOSIS, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>HOOGENBOOM H R ET AL: "Selection - dominant and nonaccessible epitopes on cell-surface receptors revealed by cell-panning with a large phage antibody library." EUROPEAN JOURNAL OF BIOCHEMISTRY, (1999 MAR) 260 (3) 774-84. , XP000978815 abstract page 774, column 1, line 1 -page 779, column 1, paragraph 1 page 780, column 1, line 1 -page 783, paragraph 2</p> <p>---</p> <p style="text-align: center;">-/-</p>	1-37

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

° Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

24 January 2001

30/01/2001

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Authorized officer

Muller-Thomalla, K

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/03900

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PILLION D J ET AL: "Immunofluorescent studies of the rat adipocyte cell surface." INTERNATIONAL JOURNAL OF IMMUNOPHARMACOLOGY, (1984) 6 (3) 193-204. , XP000978782 abstract page 193, column 2, last paragraph -page 194, column 2, paragraph 1 ---	1-37
Y	US 5 631 009 A (CRYER ANTHONY ET AL) 20 May 1997 (1997-05-20) column 9, line 4 -column 12, line 30; figure 3 ---	1-37
Y	US 5 102 658 A (FLINT DAVID J) 7 April 1992 (1992-04-07) column 2, line 47 -column 4, line 53 ---	1-37
Y	LOGTENBERG T ET AL: "Detecting novel cell surface antigens using phage antibody display" IMMUNOTECHNOLOGY, NL, ELSEVIER SCIENCE PUBLISHERS BV, vol. 2, no. 4, 1 November 1996 (1996-11-01), page 302 XP004063249 ISSN: 1380-2933 abstract ---	1-37
Y	HOOGENBOOM H R ET AL: "Antibody phage display technology and its applications" IMMUNOTECHNOLOGY, NL, ELSEVIER SCIENCE PUBLISHERS BV, vol. 4, no. 1, 1 June 1998 (1998-06-01), pages 1-20, XP004127382 ISSN: 1380-2933 abstract page 2, column 1, last paragraph -page 13, column 2, paragraph 1 ---	1-37
Y	HOOGENBOOM H R: "Designing and optimizing library selection strategies for generating high-affinity antibodies" TRENDS IN BIOTECHNOLOGY, GB, ELSEVIER PUBLICATIONS, CAMBRIDGE, vol. 15, no. 2, 1 February 1997 (1997-02-01), pages 62-70, XP004034115 ISSN: 0167-7799 the whole document ---	1-37

-/-

INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/GB 00/03900

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	<p>EDWARDS B M ET AL: "Isolation and tissue profiles of a large panel of phage antibodies binding to the human adipocyte cell surface" JOURNAL OF IMMUNOLOGICAL METHODS, ELSEVIER SCIENCE PUBLISHERS B.V., AMSTERDAM, NL, vol. 245, no. 1-2, 1 November 2000 (2000-11-01), pages 67-78, XP004218809 ISSN: 0022-1759 -----</p>	

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: Part of claims 1-17 and 20-37

The scope of part of present claims 1-17 and 20-37 relate to an extremely large number of possible compounds and methods. In fact, claim 1 and all claims related thereto contain so many options amongst the cited claimed amino acid sequences and possible combinations thereof, that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search for the first invention has been carried out for those parts of the application which could be considered to be clear and concise, namely a panel of 10 "binding members" which each contain one of the VH-CDR sequences shown in Table 4, but restricted to those VH-CDRs of the "FATs" indicated in claim 18, as well as the corresponding ten single binding members (claim 26 onwards) with the distinct VH variable domains as indicated in claim 19 (bringing the present search up to 20 distinct sequence searches in the relevant databases, namely 10 CDR3 sequences (see claim 18) and in addition the corresponding antibody VH variable domains (see claim 19)). In this context it should be noted that the present application as filed does not appear to highlight the relevance of any further combination of 10 binding partners which might be considered essential/relevant to carry out the invention. In this respect, it should also be noted that the relevance of the chosen combination as claimed in claims 18 and 19 is per se not ad hoc apparent from the description and examples of the application as filed, but was chosen as they appeared as the only specific combination of least ten binding members in the present claimed subject-matter.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 00/03900

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US 5631009	A	20-05-1997	AT 175422 T	15-01-1999
			AU 664147 B	02-11-1995
			AU 2568692 A	27-04-1993
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			GB 2259706 A,B	24-03-1993
			JP 6510780 T	01-12-1994
			NZ 244349 A	26-10-1994
US 5102658	A	07-04-1992	CA 1302319 A	02-06-1992